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Abstracts

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Poster Session 1
11:30 a.m.-6:30 p.m.

1.001

THE RELATION BETWEEN INTERICTAL SPIKES AND SEIZURES IN RAT MODELS OF EPILEPSY

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Rationale: Interictal spikes (ISs) are biomarkers for excessive brain excitability in epilepsy. However, the relationship between IS frequency and pattern and seizure development is not well understood. In some acute seizure models, ISs increase in frequency and complexity just before seizures and appear to be the triggering event. In other epilepsy models, there appears to be little relationship. In human patients, there is a suggestion that spikes increase after seizures and then decline thereafter. If there is a relationship between seizures and ISs, it is likely to be more clearly seen in animals that exhibit clustered seizures. We hypothesize that repetitive seizures increase the frequency of ISs, and the seizure clusters or ISs slowly induce a homeostatic mechanism that may end the cluster and reduce the likelihood of subsequent seizures for days or weeks.

Methods: Status epilepticus (SE) was induced in male Sprague Dawley rats by either i.p. injection of pilocarpine (n=15) or electrical stimulation of the perforant path bilaterally for 3 hours (n=8) or unilaterally for 8 hours (n=10). Animals that developed spontaneous recurrent seizures were continuously monitored with bilateral intracranial electrodes and video for periods up to 6 months. Automated spike and seizure detecting software were used for analysis, with video confirmation of seizures.

Results: Adult rats that undergo either chemically or electrically induced SE develop chronic epilepsy at various times after the inducing stimulus. ISs are invariably present in those animals that develop epilepsy. In animals that exhibit clustered seizures (n=8, clusters occur at 7-14 day intervals with 10-50 seizures per cluster), ISs are often at their lowest frequency before the seizure clusters, increase in frequency during the cluster (over 1-2 days), continue to increase in frequency after the seizures subside (over 1-2 days), and then slowly decline over several days to low levels before the beginning of the next cluster. In animals with only isolated seizures, a similar pattern can be observed.

Conclusions: Our data suggest that clusters of seizures are most likely to occur during periods of reduced IS firing. The seizures are associated with (or cause) an increased IS firing (especially during intense clusters) which may paradoxically reduce the likelihood of subsequent seizures. The time course of the phenomena in the rats with clustered seizures suggests that slow molecular events may be occurring that serve to both enhance some forms of brain excitability (ISs) while at the same time, reducing the tendency for subsequent seizures for substantial periods. It has been shown, for example, that repetitive seizures can induce normally glutamatergic granule cells to produce and secrete GABA and that this change in neuronal phenotype lasts for approximately one week. It is likely other homeostatic mechanisms are also involved in dampening excessive brain excitability. Identifying these mechanisms may provide new targets for innovative anti-seizure therapy.

1.002

THE ROLE OF ASTROCYTES IN THE EPILEPTOGENICITY OF CORTICAL MICROGYRI

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Rationale: Developmental cortical malformations including polymicrogyria and tuberous sclerosis are associated with intractable epilepsy. To understand the pathophysiology of epilepsies associated with cortical malformations, we have utilized glutamate imaging in the freeze-lesion (FL) model of polymicrogyria. In this model neurons that form deep cortical layers are lost, resulting in a microgyrus enriched in layer II/III neurons. Our preliminary findings have shown that the ability of glial cells to remove applied extracellular glutamate is altered in the FL model. Regional differences in glutamate reuptake were measured using glutamate imaging and SR101 staining was used to quantify the location of astrocytes in and around the lesion site. Immunohistochemical analysis of multiple glial cell markers was also used to examine the local density and phenotype of astrocytes in the malformed cortex.

Methods: Microgyri were created by briefly placing a freezing probe on the skulls of neonatal rat pups. Neocortical brain slices from sham operated and freeze lesioned rats were prepared 14-128 days later. Brain slices were then loaded with glutamate FRET biosensor and both images and extracellular field recordings were collected simultaneously. Brain slices were also stained with SR101, an astrocyte specific dye for use in live tissue, and maps of glial density were made using in-house imaging software.

Results: In order to thoroughly address the regional variability in glutamate reuptake capacity we locally perfused 5 mM glutamate onto the microgyral zone (MZ). Glutamate reuptake capacity was increased in the MZ itself while in areas adjacent to the MZ glutamate reuptake capacity was compromised. As predicted, glutamate reuptake capacity was directly correlated to glial cell density as measured by SR101 staining. In regions where glial cell density was highest there was a higher capacity to remove applied glutamate. This correlation was lost when TBOA, an antagonist of the plasma membrane glutamate transporters, was applied to the tissue before perfusion of glutamate. Immunohistochemical analysis of GFAP, ALDH1L1, a pan-glial marker, and GLT-1, the astrocytic glutamate transporter, was performed. Interestingly ALDLH1 and GLT-1 appear to be increased in the MZ where glutamate reuptake capacity was highest and GFAP staining was more abundant directly adjacent to the MZ, where glutamate reuptake capacity was lower.

Conclusions: Our findings indicate that there are anatomical and functional changes in astrocytes in the FL model. The decrease in glutamate reuptake capacity directly adjacent to the MZ and the increased expression of GFAP in this area suggests that reactive astrocytes cannot efficiently clear synaptically released glutamate. This may in turn lead to prolonged glutamate signaling and contribute to the hyperexcitability of the FL. The increase in astrocytic protein expression and regional glutamate uptake within the MZ, on the other hand, suggests that the increased density of glia in the MZ may contribute to more efficient glutamate clearance within this region.

1.003

GABAERGIC EXCITATION CONTRIBUTES TO SEIZURE GENERATION IN VITRO

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Rationale: Broadly speaking, anti-epileptic drugs work to either enhance inhibition (benzodiazapenes, barbiturates, etc.) or reduce excitation/excitability (phenytoin, topiramate, etc.). Studying the interactions between excitation and inhibition in neural networks has been technically challenging, limited primarily to the scale of either broad pharmacological manipulations or paired intracellular recordings. Here, we have attempted to bridge this gap, using a combination of recently developed imaging and genetic techniques, to study the pathological neuronal network dynamics that lead to seizures in acute slices of hippocampus and entorhinal cortex. Specifically, we looked at cell-type specific (interneuron vs. excitatory cell) firing patterns at seizure onset to gain insight into the interplay between inhibition and excitation.

Methods: Using a recently developed laser-scanning strategy, Targeted Path Scanning (TPS), in conjunction with two-photon excitation of bath-applied, calcium-sensitive dye, Indo-1 AM, we imaged epileptiform activity in slices of hippocampal formation from GAD67-GFP (GIN) mice. In this way, we were able to record simultaneously activity in populations of GABAergic interneurons (I-cells) and putative excitatory neurons (E-cells). We compared observed I-cell and E-cell calcium dynamics to their electrical activity by targeting simultaneous patch clamp recording to GFP+ and GFP- cells. Finally, we tested our hypothesis that GABAA synapses were driven into a depolarizing regime and contributing to seizure onset using pharmacological manipulations and a transgenic mouse, Clomeleon-1, which expresses a genetically encoded chloride sensor.

Results: At 4-AP-induced SLE onset, we observed a high amplitude pre-ictal calcium spike that is significantly larger in I-cells than it is in E-cells ($n=25$, $p<0.05$). We hypothesize that I-cells fire hard enough to become depolarizing, resulting in a positive feedback loop capable of generating seizures. Simultaneous dual patch recordings of GFP-expressing interneurons and putative E-cells confirm the elevated I-cell firing rates and reveal seemingly random firing before the I-cell-dominated pre-ictal spike. After the pre-ictal spike, however, E-cell spikes follow I-cell spikes by approximately 3ms, suggesting a monosynaptic, excitatory GABAergic connection. Furthermore, acetazolamide, a drug that hyperpolarizes the GABA reversal potential by blocking production of the depolarizing, GABA-synapse permeant ion, bicarbonate, dramatically reduces ictal-like activity. Finally, using Clomeleon mice, which express a genetically-encoded chloride sensor, we directly imaged a substantial (10-20mM) increase in intracellular chloride at SLE onset.

Conclusions: We have provided evidence that, at seizure onset, interneurons produce a large calcium transient, corresponding to elevated firing rates. This leads to postsynaptic chloride accumulation, which results in paired I-before-E action potentials. Together, these results suggest that, in the acute slice preparation, interneurons become transiently excitatory, producing a positive feedback network that contributes to SLE generation.

1.004

CHRONIC CHANGES OF REACTIVE ASTROCYTES IN RAT BRAIN FOLLOWING PILOCARPINE-INDUCED SEIZURES

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Rationale: Gliosis is a pathological hallmark of many epileptic foci. Persistent change of morphology and loss of astrocytic domain organization has been found in the epileptic brain (Oberheim, et al., 2008). However, there is little known about the functional changes of chronic reactive astrocytes. In our previous studies, we observed dramatic changes in morphology, immunohistochemical staining and electrophysiological properties of acute reactive astrocytes following pilocarpine-induced seizures. We propose that reactive astrocyte changes persist chronically, and may be important contributors to epileptogenesis.

Methods: Whole-cell patch-clamp recording was performed on astrocytes in rat hippocampus and piriform cortex one month to three month after pilocarpine-induced seizures. Intercellular gap junction coupling was examined by filling cells with 0.2% Lucifer yellow and/or 0.5% biocytin. Brain slices were fixed for further immunohistochemical staining.

Results: One to three months after pilocarpine insult, many chronic reactive astrocytes (RAs) were observed in the vicinity of brain lesions in hippocampal CA1-CA3 region and piriform cortex. Most chronic RAs were found to have fewer fine processes and enlarged branches, with a high level of GFAP expression ($n=10$). Some fibrous-like astrocytes with long, radial and non-branched extensions could also be seen in the area proximal to the brain lesion. In most chronic RAs, intercellular gap junction coupling was dramatically reduced. Resting membrane potential of chronic RAs was lower than control astrocytes. They showed passive current-voltage (IV) pattern as observed in control astrocytes. However, they had impaired glutamate transport function. Glutamate transporter current was reduced from 574.28 ± 68pA (control, $n=9$) to 163.33 ± 34.8pA ($n=6$) ($p<0.05$). We also observed some chronic RAs with a moderately high level of GFAP expression ($n=5$), but with cellular appearance similar to that of control protoplasmic astrocytes, with highly ramified, spongiform processes. These chronic RAs were coupled to surrounding cells. Their passive membrane properties were similar to control astrocytes, while glutamate transporter current was only slightly reduced in these RAs (370 ± 128.08 pA, $n=4$).

Conclusions: Our results demonstrate that morphological and physiological changes of acute severe RAs are persistent in many chronic RAs one to three months after pilocarpine insult. Some chronic RAs develop a fibrous-like cellular appearance, similar to that seen in "scar" astrocytes in human sclerotic cortical and hippocampal tissues. Our findings are consistent with acute "severe" RA cells progressing to become glial scar cells, while acute "mild" RA cells may recover morphologically and functionally over time. Further study will determine if such dynamic changes of chronic RAs can be inhibited by agents such as olomoucine or rapamycin.

1.005

HCN CHANNEL INHIBITION ENHANCES EPILEPTIFORM RESPONSES IN NEOCORTICAL NEURONS

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Rationale: Hyperpolarization activated non-selective cation (HCN) channels, expressed primarily within the distal dendrites of pyramidal neurons, have been implicated in cellular mechanisms contributing to epilepsy. Within distal dendrites, HCN channels serve to normalize the time-courses of distal excitatory inputs. Upon membrane hyperpolarization, the non-inactivating cationic current (Ih) slightly depolarizes the resting membrane potential while decreasing the input resistance. Ih inhibition can enhance summation from distal excitatory inputs and increases the spiking frequency of cells in response to depolarizing current injections. Decreased HCN channels and Ih are observed in a variety of epilepsy models. Our goal was to characterize the effect of HCN channel inhibition on evoked epileptiform activity in neocortical pyramidal cells and GABAergic interneurons.

Methods: Acute neocortical slices (300 μm) were cut from 20-28 day old rats and kept in standard ACSF at room temperature. Individual slices were transferred to a recording chamber perfused with oxygenated ACSF (3mL/min) at 32o C. Whole cell recordings were obtained from neocortical pyramidal cells and interneurons. Epileptiform activity was evoked in the presence of bicuculine (10 μM) using a bipolar stimulating electrode. Cells were identified visually, by their spiking properties and distance from the pial surface. Biocytin was included in the recording pipette for subsequent visualization. ZD-7288 (10-20 μM) was used in inhibit HCN channels.

Results: Intracortical stimulation evoked a long lasting (200-300 ms) depolarization (20-30 mV) and persistent spiking in layer V pyramidal neurons. Evoked epileptic activity in layer 1 interneurons was of similar duration (200-300 ms) but was lower in amplitude (10-20 mV) with significantly less spiking. Interneurons exhibited a late inhibitory response immediately following evoked epileptic activity. Bath application of ZD-7288 increased the duration of epileptic activity in layer V pyramidal neurons and increased the number of spikes (N = 7). Epileptic activity in layer I interneurons also exhibited significantly increased duration. Small increases in amplitude following ZD-7288 application. Furthermore, the late inhibitory response was changed to a late depolarized response in layer I cells.

Conclusions: The direct effects of HCN channel inhibition on epileptiform activity have received little attention. Our results indicate that HCN channels normally constrain polysynaptic epileptiform responses within the neocortex. Results indicate a differential effect of Ih inhibition on GABAergic interneurons versus pyramidal neurons. Pyramidal neurons exhibit increased spiking while interneurons only exhibit a prolonged depolarization. These changes could have important implications for regulation of network excitability. NS22373

1.006

ROLE OF TRKB RECEPTORS, AND PRESYNAPTIC AXONAL SPROUTING IN HYPEREXCITABILITY AFTER SCHAFFER COLLATERAL TRANSECTION AND ITS CONTRIBUTION TO POSTTRAUMATIC EPILEPSY

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Rationale: Posttraumatic epilepsy (PTE) is a common and serious complication of acute traumatic brain injury (TBI), especially after dural penetration. Seizures occur after a latent period of months to years. This delay in epileptic development suggests the initiation of a slow process after injury leading to a permanently epileptic brain. We have modeled a penetrating TBI by transecting the Schaffer collateral (SC) pathway in vivo and in vitro. These lesions have been shown previously to result in delayed axonal sprouting of CA3 pyramidal cells in vitro and an increase in the probability that CA3 cells are connected by excitatory synapses. The extent of this axonal sprouting is correlated with hyperexcitability and transgenic mice with reduced trkB expression are less likely to exhibit axonal sprouting after SC transection. We now extend these findings using mice in which a single amino acid mutation in the trkB receptor (F616A) has been knocked-in rendering it susceptible to pharmacological blockade by 1NMPP1 (Chen et al., 2005). TrkBF616A receptors are fully functional without the drug present and allow for full pharmacological blockade in the presence of the drug.

Methods: SC pathway transection was performed in hippocampal slice cultures derived from trkBF616A mice at day in vitro 14; cultures were treated with 1NMPP1 or normal media. Cultures were processed for immunohistochemical and Western blot (WB) analysis of GAP43, a marker for growing axons. In order to determine the contribution of trkB receptors and axonal sprouting under more physiological conditions, we performed SC transections in vivo in trkBF616A mice using a microknife mounted on a stereotaxic carrier. Extracellular recordings of acute physiology slices were carried out to determine hyperexcitability. WB analysis was carried out to determine GAP43 levels after lesion.

Results: Our in vitro model revealed that the number of GAP43 immunoreactive fibers in the vicinity of the lesion was significantly reduced in cultures treated with 1NMPP1, compared to untreated cultures. Blockade of the trkB receptor with 1NMPP1 prevented the increase in GAP43 protein levels that were observed after the lesion (n=4, p=0.001, ANOVA).Extracellular recording in area CA3 from acute hippocampal brain slices obtained the in vivo model showed a marked increase in their coastline bursting index indicating they were hyperexcitable (n=6, p=0.001, ANOVA). WB analysis of GAP43 levels indicated an increase GAP43 protein following the lesion as compared to sham controls (n=4, p=0.001, ANOVA).

Conclusions: We confirm our previous suggestion that lesion induced neurotrophin-trkB signaling is a critical promoter of axonal sprouting after injury. We are currently treating mice with 1NMPP1 to test the hypothesis further that trkB receptor activation is required for injury-induced axonal sprouting and hyperexcitability. These data will provide a better understanding of the role of trkB receptor signaling and axonal sprouting after TBI and PTE.

1.007

A CANDIDATE ROLE FOR ABERRANT MTOR SIGNALING IN SE-ASSOCIATED ALTERATIONS IN DENDRITIC ION CHANNEL HOMEOSTASIS

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Rationale: Recent studies have shown increased mTOR signaling in rodent models of acquired temporal lobe epilepsy (TLE). In these models the development of epilepsy occurs following a prolonged episode of status epilepticus (SE). SE is associated with significant long term morbidity, including the development of spontaneous seizures and cognitive deficits. Given that the mTOR signaling cascade modulates dendritic arborization, spine morphology, and surface expression of ion channels, we evaluated whether excessive mTOR signaling triggered by

pilocarpine-induced SE, contributes to alterations in dendritic ion channels and proteins following SE.

Methods: Male Sprague Dawley rats at postnatal day ~35 were treated with pilocarpine (Pilo) to induce 1 hr of SE. Vehicle animals (control, CTL) were processed in parallel. After 2 weeks, rapamycin (Rap; 6mg/kg) or vehicle, was administered by intraperitoneal injection every other day for 1 week to suppress mTOR activation in sham (Rap alone) and pilocarpine treated rats (Pilo + Rap, or Pilo + Veh). We used western blotting (WB, n = 5-8 / group) and immunohistochemistry (IHC, n = 3-4 / group) to evaluate hippocampal protein levels and distribution of S6, 4E-PB1, MAP2, Kv4.2, HCN1 and SK2 channels 3 weeks after SE.

Results: We confirmed SE-induced hyperactivation of mTOR signaling based on increased phosphorylation of the mTOR downstream targets, S6 and 4E-PB1 ($p < 0.05$). WB showed a significant reduction in the protein levels of MAP2, Kv4.2, HCN1 and SK2 in Pilo compared to CTL hippocampi ($p < 0.5$). IHC showed a loss of MAP2-stained dendrites, and reduced signal of MAP2, Kv4.2, HCN1 and SK2 within the CA1 dendritic fields of Pilo compared to CTL hippocampi ($p < 0.05$). Rapamycin treatment reversed these changes.

Conclusions: Our findings suggest that SE-induced hyperactivation of the mTOR pathway contributes to altered dendritic ion channel homeostasis following SE and suggests a therapeutic role for mTOR inhibition following SE.

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1.008

CHANGES IN ACTION POTENTIAL FEATURES CORRELATE WITH DIFFERENT PHASES OF FOCAL SEIZURE DISCHARGES IN THE ENTORHINAL CORTEX

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Rationale: Focal seizures correlate with stereotyped electrophysiological patterns that can be reproduced in animal models. The analysis of the cellular and network changes that subtend these patterns contribute to the understanding of ictogenesis. We recently demonstrated that seizure onset in an in vitro model of focal seizures correlates with a complete interruption of neuronal firing in principal neurons, that resumes within 5-10 seconds (Gnatkovsky et al. 2008). We test here the hypothesis that ectopic firing induced by elevations of extracellular potassium is responsible for progression of seizure synchronization.

Methods: We analyzed seizure-like discharges generated in the entorhinal cortex of the in vitro isolated guinea pig brain preparation by 3-minute applications of the GABAA receptor antagonist, bicuculline. We focussed our investigation on the features of action potentials recorded in principal neurons and interneurons recorded intracellularly with sharp electrodes.

Results: Analysis of phase plots of action potentials (dV/dt versus voltage) was utilized to characterize threshold, amplitude and repolarization features of spikes in the different phases of the seizure-like discharge. During the transition toward the extracellular irregular spiking, action potential firing resumed in principal cells: in layer II-III neurons spikes showed higher threshold, lower peak amplitude and faster repolarization compared to pre-ictal spikes. These action potentials could be interpreted as ectopic spikes. Spike doublettes characterized by a second action potential with features of calcium spike were also observed. Within few seconds, burst firing emerged and become progressively more regular. Changes in action potential features correlate with increases in extracellular potassium concentration.

Conclusions: Analysis of action potential features contributes to the understanding of the mechanisms of focal seizure generation and progression. Ectopic firing, possibly due to enhancement of potassuim concentration plays a primary role in focal seizure development.

1.009

PROLONGED CANNABINOID EXPOSURE ALTERS GABAA RECEPTOR MEDIATED SYNAPTIC FUNCTION IN CULTURED HIPPOCAMPAL NEURONS

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Rationale: A growing interest in developing cannabinoid based medication along with marijuana's recreational use makes it important to investigate molecular adaptations the endocannabinoid system undergoes following prolonged use and withdrawal. Repeated administration and prolong exposure to cannabinoids results in development of tolerance to its physiological effects and produces clinically relevant withdrawal symptoms that include irritability, restlessness and occasionally seizures. Laboratory studies have also indicated enhanced CNS excitability following cannabinoid withdrawal.

Methods: To identify mechanisms responsible for this increased neuronal excitability we employed electrophysiological and immunocytochemical techniques to investigate effects of prolonged cannabinoid type-1 receptor (CB1) agonist exposure on cultured hippocampal neurons. Neuronal cultures were exposed to the cannabinamimetic (+WIN or -WIN) at 1 uM concentration in maintenance medium for 24-h. At the end of this period, +/- WIN was removed and cultures were immediately utilized for experimentation. Miniature inhibitory postsynaptic currents (mIPSCs) were recorded using whole-cell voltage-clamp technique. Hippocampal neuronal cultures were also evaluated immunocytochemically for membrane CB1, GABAA receptor and markers for inhibitory and excitatory synapses.

Results: CB1 co-localized extensively at GABAergic synapses in our neuronal preparations. Prolonged exposure and subsequent withdrawal of the CB1 agonist WIN 55212-2 (+WIN 1uM, 24-h) produced neuronal hyperexcitability. Prolonged +WIN exposure caused profound CB1 downregulation (87%) that was accompanied by an increased GABA release as indicated by increased mIPSC frequency (2-fold), a diminished GABAergic inhibition as indicated by a reduction in mIPSC amplitude (40%) and a reduction in GABAA channel number (45%). Immunocytochemical analysis demonstrated a decrease in surface GABAA â2/3 receptor subunit expression (25%) but no change in vesicular GABA transporter following +WIN (1uM, 24-h) suggesting that even though GABAA receptors are downregulated, the GABAergic terminals remained intact.

Conclusions: This study demonstrates that prolonged cannabinoid exposure is associated with profound downregulation of CB1. Subsequent withdrawal following prolonged CB1 agonist exposure results in massive neuronal hyperexcitability. This hyperexcitability observed following agonist-induced downregulation of the CB1 may result from alterations in both presynaptic GABA release mechanisms and postsynaptic GABAA receptor function, thus demonstrating a novel form of cannabinoid mediated neural plasticity.

1.010

ALTERED GABA SIGNALING IN THE ACUTE HIPPOCAMPAL SLICE MODEL OF BRAIN TRAUMA

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Rationale: Traumatic brain injury is often complicated by early seizures occurring within the first week after injury. These early seizures may exacerbate the brain injury increasing the risks for development of epilepsy. The mechanisms underlying early post-traumatic seizures remain unknown.

Methods: High resolution two-photon fluorescence chloride imaging and simultaneous non-invasive extracellular field potential recordings of multiple unit activity (MUA) and synchronous population activity were performed in the intact hippocampus and acute hippocampal slices in vitro of the neonatal (postnatal day (P) 5-7) transgenic mice CLM-1 expressing Clomeleon. Acute hippocampal slices were used as a model of severe traumatic brain injury. Age-matched intact hippocampal preparations from the same animals were used as controls. Simultaneous extracellular field potentials of multiple unit activity from hundreds of neurons were performed to determine whether the net responses to $GABA_A$ receptor modulators are excitatory or inhibitory.

Results: Using two-photon microscopy and the genetically expressed chloride fluorophore Clomeleon, we found that neurons in brain slices from neonatal CLM-1 mice exhibit a profound accumulation of $[Cl^-]_i$, resulting in long-term shift in the reversal potential for $GABA_A$ receptor mediated responses (E_{GABA}). The $[Cl^-]_i$ accumulation inverted the net operation of $GABA_A$-receptor from inhibition to excitation. There was a very strong correlations between neuronal $[Cl^-]_i$ and proximity to the slice surface. The $[Cl^-]_i$ of many morphologically normal neurons near the surface was high enough to cause E_{GABA} to be positive to action potential threshold. For the cells with highest $[Cl^-]_i$ (> 100 mM) there was also a strong correlation between $[Cl^-]_i$ and neuronal volume, with large swollen cells exhibiting $[Cl^-]_i$ close to the chloride concentration of the extracellular solution. There was also a strong correlation between neuronal $[Cl^-]_i$and the probability of apoptosis as assayed by fluorescent indicator of caspase activation (FLICA). Inhibition of neuronal NKCC1-mediated inward chloride transport with the diuretic bumetanide did not reduce $[Cl^-]_i$ in the most of large swollen neurons.

Conclusions: Our results provide a possible mechanism for early pathological GABA-mediated excitation after traumatic brain injury. We are currently investigating the long-term chronic effects of neuronal trauma and intracellular chloride accumulation on development of spontaneous epileptiform discharges and anticonvulsant resistance.

1.011

NEUROSTEROID WITHDRAWAL INCREASES THE GABA-A RECEPTOR DELTA-SUBUNIT EXPRESSION AND ANTISEIZURE SENSITIVITY OF NEUROSTEROIDS

Omkaram Gangisetty and D. Reddy (Neuroscience and Experimental Therapeutics, Texas A&M Health Science Center, College Station, TX)

Rationale: Neurosteroids are endogenous regulators of seizure susceptibility especially in conditions such as catamenial epilepsy, a neuroendocrine condition in which seizures are clustered around specific points in the menstrual cycle. Neurosteroids regulates GABA-A receptor plasticity. Neurosteroid withdrawal such as that occurs during menstruation is associated with marked increase in expression of GABA-A receptor á4-subunit, but alterations in ä-subunit was not completely characterized. Moreover, the molecular mechanisms underlying neurosteroid withdrawal induced alterations in subunit composition remains unclear.

Methods: In this study, we determined neurosteroid withdrawal induced alterations in the ä-subunit expression in the hippocampus using a mouse withdrawal paradigm. The role of progesterone receptors (PRs) was investigated utilized the progesterone receptor knockout (PRKO) mice. Animals were treated with progesterone (25 mg/kg, bid x 7 days) and then on day 7 were treated with finasteride (50 mg/kg), which causes neurosteroid withdrawal by blocking conversion of progesterone into neurosteroids. Fully hippocampus-kindled mice were utilized to assess the antiseizure sensitivity of neurosteroids during neurosteroid withdrawal.

Results: Neurosteroid withdrawal induced a twofold increase in ä-subunit mRNA expression in WT mice, but this upregulation was undiminished in PRKO mice. Neurosteroid withdrawal-induced ä-subunit upregulation was associated with enhanced antiseizure sensitivity of the neurosteroid allopregnanolone and significant reduction in the antiseizure sensitivity of the benzodiazepine diazepam.

Conclusions: These results indicate that neurosteroid withdrawal-induces upregulation of GABA-A receptor ä-subunit expression in the hippocampus via a PR-independent signaling pathway. The enhanced neurosteroid sensitivity observed during neurosteroid withdrawal may be due to increase in abundance of ä-containing receptors in the hippocampus. *Supported by NIH grant NS051398*

1.012

WP1066 SLOWS THE PROGRESSION OF PILOCARPINE-INDUCED EPILEPSY BY INHIBITING THE PHOSPHORYLATION OF STAT3

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Rationale: Pilocarpine-induced status epilepticus (SE) activates the JAK/STAT pathway in the dentate gyrus (DG) of the hippocampus. Decreased transcription of $GABA_A$ receptor á1 subunit (GABARá1) after SE is mediated by ICER and phosphorylated cAMP response element-binding protein (CREB) binding to the GABARá1 CRE site. Infusion of pyridone 6 (P6), a pan-JAK inhibitor, blocks JAK/STAT pathway activation after SE as shown by the absence of increases in pSTAT3 protein levels, blockage of increases in protein and mRNA expression of inducible cAMP early repressor (ICER), and the consequential reduction in downregulation of the á1 subunit in the DG. These distinctive properties suggest that JAK/STAT inhibitors may be a novel addition to current therapy for refractory seizures, which occur in ~40% of temporal lobe epilepsy (TLE) patients.

Methods: Four weeks after SE was induced, epileptic rats were sacrificed within 3-4 hours after a spontaneous seizure to determine protein levels of ICER and pSTAT3 in microdissected DG of hippocampus. To further evaluate the potential disease modifying effects of JAK/STAT inhibitors, SE rats (i.e., pooled SE only (n=2) and SE +DMSO (n=7)) were compared to SE rats treated with 50 mg/kg WP1066 i.p. at onset of SE and 50-100 mg/kg WP1066 i.p. 1 hour after SE onset (n=4).

Results: Current studies demonstrate that spontaneous recurrent seizures that define chronic epilepsy "reactivate" the JAK/STAT pathway, specifically that increased levels of pSTAT3 are expressed in the DG within 3 hours of a spontaneous seizure in pilocarpine-treated rats 4 weeks after SE relative to control rats that received a subconvulsive dose of pilocarpine, did not experience SE, and did not have spontaneous seizures. Increased levels of ICER protein expression were also observed in the DG of chronically epileptic rats sacrificed within 3 hours of a spontaneous seizure when compared to age-matched controls without spontaneous seizures, but this was not a statistically significant difference. WP1066 administration (i.p.) at the onset of SE effectively blocked increases in pSTAT3 in DG 6 hrs after SE onset. Continuous video-EEG monitoring for two weeks demonstrated that administration of i.p. WP1066 at onset of pilocarpine-induced SE significantly reduces the duration of SE 3-fold and impedes the progressive increase in spontaneous seizure number over time observed in SE only and SE+DMSO rats. Latency to first seizure was not affected by WP1066 administration; and the first spontaneous seizure appeared at 3-7 days after SE for untreated rats or rats treated with DMSO and 4-9 days after SE for WP1066 treated rats.

Conclusions: This data suggests that 100-150 mg/kg total WP1066 treatment at SE potentially reduces the severity and duration of SE, and slows the acquisition of increasing seizure frequencies over time inherent to post-SE models, suggesting that JAK/ STAT inhibitors may reduce the progression of epileptogenesis and be disease modifying. Continuous video-EEG monitoring from SE for a longer duration with more animals is required to further evaluate this hypothesis.

1.013

HIPPOCAMPAL INTERNEURONS INCREASE FIRING RATE AT THE ONSET OF SPONTANEOUS SEIZURES IN AN AWAKE, FREELY MOVING RAT MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: The behavior of populations of hippocampal neurons and their interactions are important for understanding the process of seizure generation in temporal lobe epilepsy. Hyperexcitability in hippocampal networks has long been thought to be a mechanism for the initiation of spontaneous seizures. However, more recently the role of inhibition in this process has been investigated, especially for seizures with low-voltage fast (LVF) activity near the onset.

Methods: To investigate this, a rat model of chronic epilepsy was employed, with pilocarpine as the agent used for induction of status epilepticus. In the months following status epilepticus, spontaneous seizures were observed to occur with an approximate frequency of 4 per week. At this time, rats were implanted with 7 drivable tetrodes which were slowly advanced into the CA3 field of the hippocampus. Broadband signals (0.8 Hz - 6.5 kHz) were amplified using a 31 channel wireless headstage, sampled at 40 kHz and stored along with video recordings. Features extracted from the action potential waveforms were automatically clustered and final single neuron discrimination was done manually. Pyramidal cells were differentiated from interneurons on the basis of firing rate, waveform shape, and autocorrelation. To gain insight into the process of seizure generation, we examined the average firing rate and spike field coherence of these two populations of neurons during the 2 hours leading up to each seizure onset. The baseline mean and standard deviation of these measures were obtained from the time period starting 2 hours prior to seizure onset and ending 1 minute before onset.

Results: The majority of seizures (> 50%) were preceded by LVF activity, which began with an LFP spike and slow wave 5-10 seconds prior to the first appearance of large amplitude ictal spiking. These seizures (n = 18) were used for further analysis. The period of time between the initial slow wave and the start of ictal spiking was accompanied by a significant ($p < 0.05$) increase in interneuron firing rate for all seizures in the analysis. This increase was, on average, greater than 2 times the baseline interneuron firing rate. Firing rate remained elevated until the appearance of the large amplitude ictal spikes, then decreased below baseline mean for the duration of seizure. Pyramidal cell firing rates decreased significantly while interneuron firing rates were high, but rebounded as ictal spiking began. Interneuron action potential times also showed an increased coherence with LFP oscillations in the frequency bands of either 10-30 Hz, 60-150 Hz, or sometimes both, suggesting increased synchrony during the period of elevated activity.

Conclusions: These data are consistent with recent seizure generation hypotheses that synchronized interneuron networks play a role in the recruitment of synchronously firing pyramidal cells in some types of temporal lobe epilepsy seizures.

1.014

MTOR INHIBITION HAS POTENTIAL ANTIEPILEPTOGENIC EFFECTS IN A CONTROLLED CORTICAL IMPACT MODEL OF TRAUMATIC BRAIN INJURY

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Rationale: Traumatic brain injury (TBI) is a major cause of disability and death. TBI is often accompanied by the subsequent development of posttraumatic epilepsy (PTE). Seizures of PTE are frequently intractable to available treatment options and attempts at preventing PTE have been unsuccessful. Understanding basic mechanisms of posttraumatic epileptogenesis is important for developing antiepileptogenic therapeutic approaches to PTE. The mammalian target of rapamycin (mTOR) pathway has been implicated in mediating mechanisms of epileptogenesis in other models of epilepsy and has also been reported to be activated in models of TBI. In this study, we tested the hypothesis that mTOR inhibition may have antiepileptogenic actions in the controlled cortical impact (CCI) model of experimental TBI.

Methods: Adult male CD-1 mice received a craniotomy and a single episode of TBI to left lateral cortex using an electromagnetic CCI device with an injury depth of 2.0 mm. Control mice received sham surgery with a left craniotomy only. Rapamycin (6mg/kg/d, i.p.) or vehicle was initiated 1 hour after TBI and continued for 3 weeks. Western blot analysis of P-S6 expression in left hippocampus and neocortex was performed at various time points (1h, 3h, 6h, 24h, 3d, 1w, 2w, 3w) after TBI or sham surgery, and effects of rapamycin versus vehicle on P-S6 expression was also tested at 6h and 3d after TBI. Histological analysis of neuronal death by Fluoro-Jade B staining and mossy fiber sprouting by Timm's staining was performed at 3d and 1w, respectively, after sham surgery or TBI in vehicle- and rapamycin-treated mice. Video-EEG recordings monitored for seizures up to 16 weeks after TBI in vehicle- and rapamycin-treated mice.

Results: mTOR pathway activation, as reflected by P-S6 expression, was significantly increased following TBI in both hippocampus and neocortex. This increase in P-S6 expression started at 3h, peaked at 6h and then decreased within 1w, returning to baseline by 2w after TBI. Rapamycin, administered after TBI, significantly blocked mTOR

activation at 6h and 3d, and decreased neuronal death and mossy fiber sprouting in hippocampus. Initial video-EEG studies suggest that rapamycin decreases the development of spontaneous seizures during the first couple of months following TBI, although continued monitoring is ongoing to determine the long-term effects of rapamycin on PTE.

Conclusions: The mTOR pathway is strongly activated following experimental TBI and may mediate mechanisms of epileptogenesis in the CCI model of TBI. The mTOR inhibitor rapamycin may have antiepileptogenic effects in this model. Supported by NIH NS056872.

1.015

TRANSGENIC OVER-EXPRESSION OF CYCLOOXYGENASE-2 (COX-2) IN NEURONS SUPPRESSES PENTYLENETETRAZOLE (PTZ)-INDUCED ACUTE SEIZURE ACTIVITY AND KINDLING ACQUISITION

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Rationale: COX-2 catalyzes the initial step in the metabolism of free arachidonic acid to lipid mediators, such as prostaglandins (PGs). In the normal central nervous system (CNS), COX-2 is localized to the cell soma and dendritic arbors of certain glutamatergic neurons and its level of expression and activity are coupled to excitatory neurotransmission. Under conditions of excess excitation, such as that associated with acute convulsive seizure activity, COX-2 activity appears to serve a suppressive role. On the other hand, COX-2 activity facilitates synaptic plasticity and, thus, has been posited to play a permissive role in epileptogenesis. However, this notion remains controversial. Previous studies have employed pharmacological inhibitors or traditional gene-deletion approaches to address the role of COX-2 in epileptogenesis. The goal of this study was to reassess this possibility using a targeted transgenic (TG) over-expression approach.

Methods: High-level constitutive expression of a human COX-2 transgene was targeted to neurons using a well-characterized Thy-1 promoter construct. The TG line employed herein (L300, C57BL/6) exhibits broad neuron-specific expression of human COX-2 protein and has ~10-fold higher basal PG levels in the CNS than non-TG littermates (Vidensky et al., *NeuroMol Med* 3:15-27, 2003). Acute seizure activity and kindling acquisition induced by the chemoconvulsant, (PTZ), were compared in TG and non-TG littermate controls.

Results: Consistent with the conclusion that PGs suppress excessive neuronal activity during excessive acute seizure activity, the incidence of PTZ-induced convulsive seizures was markedly less in TG mice over-expressing human COX-2 in neurons compared to non-TG littermate controls. Only 2/17 TG vs. 14/20 non-TG mice exhibited convulsive seizure behavior after 32mg/kg PTZ, i.p. With regard to epileptogenesis, both the median time to onset of kindling (i.e., first convulsive seizure) and latency to kindling acquisition (i.e., forth convulsive seizure) induced by daily administration of 28mg/kg PTZ i.p. were significantly delayed in TG mice. Thus, kindling onset was 5 vs. 3 days and acquisition was 9 vs. 7 days for TG vs. non-TG mice, respectively (Mann-Whitney test $P = 0.039$ and 0.028, respectively; $N = 18$-21). Although kindling acquisition was delayed at this dose of PTZ, all TG mice became kindled within 21 days. However, results from a preliminary study using a kindling dose of 24 mg/kg PTZ showed that 0/3 TG mice became kindled compared to 3/4 non-TG littermates.

Conclusions: These results suggest that neuronal COX-2 serves to suppress excessive excitation induced by an acute convulsive stimulus and offer compelling evidence that this elevation of acute seizure threshold antagonizes kindling acquisition; hence, *neuronal* COX-2 activity may function as an important endogenous neuromodulator that suppresses the process of epileptogenesis. (Supported by NIH NS056304)

1.016

HYPOXIA INDUCED EARLY LIFE SEIZURES LEAD TO INCREASED ABERRANT CA3 MOSSY FIBER SPROUTING WITH NO ASSOCIATED CELL DEATH

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Rationale: Hypoxic ischemic encephalopathy (HIE) is one of the leading cause of neonatal seizures. Approximately 35-40% of infants who experience neonatal seizures develop cognitive disabilities and or epilepsy later in life. Using a rodent model of graded global hypoxia-induced seizures in postnatal day (P)10 Long-Evans rats, we have previously shown increased hippocampal hyperexcitability, long-term cognitive deficits and development of spontaneous seizures later in life following early life seizures. To determine whether there are morphologic correlates to the spontaneous seizures in adulthood, we investigated whether hippocampal mossy fiber (MF) or other aberrant axonal sprouting occurs in this model, as other early life seizure models have reported this phenomenon in area CA3 of hippocampus (Huang et al 1999).

Methods: Long Evans rat pups were subjected to hypoxia induced seizures at P10 and were allowed to survive to adulthood. Adult rats were subsequently perfused at P100 for Timm silver staining, which labels high concentrations of Zn^{2+} found in the axonal terminals at synapses; littermate controls were used for comparison. Using the methods of Holmes et al (1999), both a semiquantitative scale and measurements of the optical density of Timm-stained axonal terminals were measured by a blinded investigator to assess change in amount of sprouting in s. pyramidale of CA3. To test if the increase in sprouting was associated with acute cell death, Fluoro-Jade B immunostaining was performed in rat pups perfused 24 and 48 hours following P10 hypoxia induced seizures.

Results: Semiquantitative scoring showed that MF sprouting in s. pyramidale of CA3 increased significantly in hypoxic animals (2.708 ± 0.137; $n=7$) compared to the control group (2.093 ± 0.114; $n=8$; $p < 0.001$). Optical density scores confirmed this significant increase in MF sprouting of the hypoxic animals (184.4 ± 15.3 %; $n=4$) when normalized to the control group (100.0 ± 9.86 %; $n=5$; $p < 0.001$). The aberrant sprouting of mossy fibers was predominantly observed in the CA3 region, no significant difference was elucidated in the dentate gyrus. Fluoro-Jade B staining showed no significant difference between hypoxic animals ($n=8$) and littermate controls ($n=4$).

Conclusions: These results suggest that hypoxia induced neonatal seizures lead to increased hippocampal connectivity through increased aberrant CA3 s. pyramidale sprouting, with no associated acute cell death. These data suggest that after neonatal seizures and in the absence of cell death, later life spontaneous seizures are associated with an increase in CA3 MF sprouting. Adult models of epilepsy have supported the hypothesis that MF sprouting may enhance positive feedback to excitatory neurons in the hippocampus to induce network hyperexcitability. Similar mechanisms may be involved in promoting

hippocampal hyperexcitability and epileptogenesis following early-life seizures.

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1.017

EARLY-LIFE SEIZURES LEAD TO INCREASED AMPA SUBUNIT-CONTAINING SYNAPSES AND HIGHER CA2+ RESPONSES IN RAT PYRAMIDAL CA1 NEURONS

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Rationale: Hypoxia is the leading cause of perinatal seizures, affecting 1-3% of infants. In rats at postnatal day (P)10, hypoxic seizures (HS) lead to increased seizure susceptibility and neurobehavioral deficits later in life, as well as hyperexcitability in hippocampal area CA1 (Jensen et al 1998) and in vivo spontaneous seizures (Rakhade et al SFN 2008). Whole-cell patch clamp recordings in CA1 neurons show a decrease in functionally silent, NMDA-receptors (NR) only containing synapses within 48hrs of HS at P10 (more AMPA receptor (AMPAR) functional synapses, Zhou et al SFN 2008). HS also downregulates GluR2 expression, increasing calcium (Ca2+) permeability in AMPARs (Koh et al 2004, Rakhade et al 2008). Here we aimed to determine 1) if we could identify the alteration in "silent synapses" morphologically, and 2) whether seizure-induced changes in synaptic AMPARs alters the functional Ca2+ response of CA1 pyramidal neurons.

Methods: Seizures in P10 rats were induced by global hypoxia. To study morphology, brain sections from P12 rats 48hrs post-HS were triple-labeled with NR subunit NR1, AMPAR subunit GluR1, and presynaptic marker synaptophysin (syn). After confocal microscopy (blinded) of CA1 s. radiatum, we counted NR1 puncta, syn puncta in contact with NR1, and GluR1 puncta in contact with NR1/syn. We used the ratio of NR1/syn-only puncta to NR1/GluR1/syn puncta to assess the % silent/total NR1 synapses. To examine Ca2+ responses due to changes in AMPAR expression, slices from rats 48hrs post-HS were labeled with ratiometric Ca2+ indicator dye Fura-2. During wide-field time-lapse imaging, slices were stimulated with kainate (KA), then treated with 150uM n-acetyl spermine (NASP), and exposed to kainate again.

Results: At 48hrs post-HS, the ratio of NR1-only to NR1/GluR1 synapses was significantly reduced by 45% in the s. radiatum of CA1 compared to age-matched controls (4.7±2.6 post-seizure, 8.6±3.5 in controls; n=4 rats/group; p=0.003). Fura-2 imaging in the same area of CA1 in live slices from rats 48hrs post-HS, revealed that peak Ca2+ change from baseline was significantly higher in pyramidal neuron somas compared to controls after a low (2.5uM, 8% mean increase, p=0.016, n=5 rats/group) or high (50uM, 17% increase, n=6 rats/group; p=0.008) KA bath application. NASP, which specifically blocks GluR2-lacking AMPARs, diminished the increased Ca2+ response to 50uM KA in slices from post-HS rats (2% increase post-HS, p=0.25, n=3/group).

Conclusions: These results suggest that within 48hrs of neonatal seizures, AMPAR subunit incorporation increases at glutamate receptors containing NRs, corroborating our previous electrophysiology findings. Further, this results in a functional increase in Ca2+ response to stimulation with KA, consistent with our prior studies showing reduced GluR2 subunits. Together, this suggest that changes in synapse function during this critical period of synaptic development in early life may contribute to epileptogenesis and cognitive dysfunction seen in this model of neonatal seizures.

RO1NS31718, DP10D003347, F32NS068161, P30HD18655

1.018

KAINATE-INDUCED STATUS EPILEPTICUS ALTERS BDNF GENE EXPRESSION IN AREA CA1 AND MEMORY FORMATION USING EPIGENETIC MECHANISMS

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Rationale: Brain-derived neurotrophic factor (BDNF) has been identified as a possible molecular mediator in epileptogenesis and in memory formation. However, little is known about the regulation of the bdnf gene in the CNS. We hypothesize that aberrant expression of memory-related genes, such as bdnf, contribute to deficits in hippocampus-dependent long-term memory formation associated with prolonged seizure activity. The studies presented here expand on the idea that epigenetics, a new molecular mechanism for gene expression changes in the nervous system, may play a role in memory disorders associated with epilepsy. For our studies we focused on area CA1 of hippocampus, a brain region well-characterized in the process of contextual long-term memory storage.

Methods: First, we determined the pattern of post-translationally modified histones (Chromatin Immunoprecipitation) and DNA methylation (Bisulfite Sequencing) at the bdnf gene in area CA1 of hippocampus after 1 h of kainate (KA)-induced status epilepticus (SE). We next determined the expression of exon-specific bdnf mRNA levels in hippocampus following KA-SE. Finally, using a contextual fear conditioning learning paradigm, we assessed the effect of histone deacetylase inhibition (HDACi) on long-term memory formation in epileptic animals (2-3 months post-SE).

Results: Quantitative real-time PCR revealed significant increases in exons I, II, IV, VI and IX bdnf mRNA levels in area CA1 of hippocampus at 1 h of KA-SE. These results support previous findings that exon-specific bdnf gene regulation occurs in hippocampus following KA-SE. Interestingly, we found that alterations in hippocampal bdnf mRNA levels correlated with DNA methylation changes at the bdnf gene during SE. Specifically, we observed demethylation of the bdnf gene at a CpG island within bdnf promoter 4 in area CA1 after 1 h of KA-SE. Next, we examined whether histone modifications at bdnf promoters, another epigenetic mechanism directly implicated in bdnf gene regulation, was altered in area CA1 of hippocampus during SE. We found that both histone H3 acetylation and phosphoacetylation levels increased at bdnf promoter 4 in area CA1 of hippocampus after 1 h of KA-SE. Moreover, HDACi with sodium butyrate significantly altered SE-induced bdnf gene expression changes in area CA1 of hippocampus at 1 h or 24 h after KA-SE and HDACi significantly enhanced long-term memory formation in epileptic animals.

Conclusions: Together our findings suggest that epigenetic regulation of the bdnf gene during epileptogenesis, mechanistically via histone modification and DNA methylation, may mediate long-lasting behavioral changes in epilepsy. Indeed, our present findings suggest that HDACi improves fear memory processing in animals that had experienced epilepsy. Additional studies are underway for assessment of altered DNA methylation patterns at the bdnf promoters in hippocampus during fear memory consolidation after KA-SE.
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1.019

THE ANTIEPILEPTIC EFFECT OF A KETOGENIC DIET IS MEDIATED BY ADENOSINE A1 RECEPTORS

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Rationale: The ketogenic diet is a high-fat, low-carbohydrate regimen that reduces seizures through as yet ill-defined mechanisms. This metabolic therapy can be effective in medically refractory epilepsy, suggesting that a ketogenic diet achieves its anticonvulsant effects via mechanisms other than those targeted by traditional antiepileptic drugs. Adenosine is an endogenous anticonvulsant and a key link between metabolism and neuronal activity. Similar to a ketogenic diet, adenosine can stop pharmacoresistant seizures. We hypothesized that adenosine acting via inhibitory adenosine A1 receptors (A1Rs) plays a key role in the anticonvulsant effects of a ketogenic diet.

Methods: To test this hypothesis, we used three types of transgenic mice, all with spontaneous electrographic seizures that are due to decreased A1R signaling: (1) mice with a complete absence of A1Rs (A1R-/-); (2) mice with a significant reduction in A1Rs (A1R+/-, a heterozygote with 50% of normal A1R levels); and (3) mice with a transgenic overexpression of adenosine kinase (Adk-tg), an intracellular enzyme that serves as a major negative regulator of extracellular levels of adenosine. Intrahippocampal electrodes recorded seizure frequency and duration after 3 weeks of maintenance on either a control or a ketogenic diet. To determine the extent to which changes in the frequency and duration of spontaneous seizures were due specifically to the low carbohydrate nature of the KD, we administered intraperitoneal injections of a 30% glucose solution.

Results: In transgenic mice with spontaneous recurrent seizures due to an adenosine deficiency but with intact A1Rs (Adk-tg), a ketogenic diet nearly abolished spontaneous seizures and reduced their duration significantly. In contrast, spontaneous recurrent seizures triggered by reduction or deletion of A1Rs were partly or completely resistant to ketogenic diet therapy, respectively. In mice which displayed reduced seizures after KD treatment we found that an injection of glucose restored seizure frequency to normal levels within 30 to 90 minutes.

Conclusions: These data suggest that a ketogenic diet reduces seizures by increasing A1R-mediated inhibition, and that this effect depends on the low carbohydrate nature of the diet. Revealing an A1R-dependent component provides new insight into the anticonvulsant mechanisms underlying the anticonvulsant effects of a ketogenic diet. Furthermore, these results suggest that ketogenic metabolism increases the activity of adenosine at the A1 receptor subtype, and could offer insight into therapies for other clinical conditions where adenosine is known to have clinical benefits.

1.020

TRANSIENT GROUP I METABOTROPIC GLUTAMATE RECEPTOR ACTIVATION ENHANCES CA3 EXCITATORY SYNAPTIC NETWORK ACTIVITY

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Rationale: Following transient exposure to the group I metabotropic glutamate receptor (mGluR) agonist dihydroxyphenylglycine (S-DHPG), the CA3 region displays long-lasting network activity that is epileptiform in character and mimics interictal and ictal synchronization. Following DHPG exposure, CA3 pyramidal neurons show a change in membrane properties that include the presence of a voltage dependent cation current and loss of the currents that underlie the medium and slow afterhyperpolarizations. We evaluated spontaneously occurring post synaptic currents (PSCs) and miniature PSCs in CA3 neurons from control slices and in slices that had been transiently exposed to DHPG.

Methods: Hippocampal slices were prepared from 10-15 day old Sprague-Dawley rats and slices were either incubated in control artificial cerebrospinal fluid (aCSF) or aCSF with 50 ìM S-DHPG for 60-120 minutes. Slices were transferred to a submerged chamber to visualize CA3 neurons using diffusion interference contrast infra-red techniques. CA3 neurons were recorded from using cesium methane sulfonate containing electrodes. Spontaneously occurring excitatory PSCs (EPSCs) were recorded at -70 mV and inhibitory PSCs (IPSCs) were recorded at 0 mV. Following these recordings, tetrodoxin (1 ìM) was added to the aCSF and miniature IPSCs and EPSCs were recorded.

Results: Neurons from slices that were exposed to DHPG had a significant increase in the frequency (median of 1.1 vs. 5. 6 Hz, $p < 0.001$, $n = 18$ control and 17 for DHPG exposed) and amplitude (18.2 ± 1.2 vs. 23.7 ± 1.7 pA, $p = 0.01$) of sEPSCs. Spontaneously occurring IPSCs tended to be more frequent in DHPG-exposed neurons (median of 5.5 vs. 8 Hz, $p = 0.06$, $n = 13$ for control and 14 for DHPG exposed), and had a trend toward lower amplitudes in neurons from slices that had been DHPG-exposed (median of 27.9 vs. 23.2, $p = 0.08$). Miniature EPSCs recorded from CA3 neurons had similar amplitudes of currents (15.7 ± 1.5 vs. 14.9 ± 0.9 pA) but occurred less frequently in slices that had been exposed to DHPG (median 0.3 vs. 0.1, $p = 0.033$). mIPSCs tended to occur less frequently (median of 0.95 vs. 0.6 Hz, $p = 0.09$) and were smaller in amplitude (19.6 ± 1.0 vs. 15.8 ± 0.8 pA, $p = 0.007$) in slices that had been exposed to DHPG.

Conclusions: Our results demonstrate that DHPG exposure produced an increase in network driven EPSCs both in terms of amplitude and frequency compared to IPSCs. These changes favor abnormal synchronous activation of pyramidal neurons and epileptiform activity. At a miniature PSC level, both mEPSCs and mIPSCs showed a decrease in frequency in slices exposed to DHPG, suggesting a presynaptic alteration that depresses release. The reduction in mIPSC amplitude following DHPG exposure suggests a post synaptic change in GABA receptors. Following transient DPHP exposure, a long-lasting change in network excitability occurred that can be explained by enhanced excitatory and decreased inhibitory neuronal activity.

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1.021

PHARMACOLOGICAL INHIBITION OF INTERLEUKIN-1â AND CYCLOOGENASE-2 DECREASES SEIZURE FREQUENCY AND MOSSY FIBER SPROUTING IN THE PILOCARPINE MODEL OF EPILEPSY

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Rationale: There is growing evidence that neuroinflammation represents both a hallmark and a mechanistic factor of chronic epilepsy.

For example, both the activation of an inflammatory cytokine Interleukin-1â and its receptor and of Cycloogenase 2 (COX-2), the rate limiting enzyme in prostaglandin synthesis, have been implicated in epileptogenesis following status epilepticus (SE). Previous studies from our group showed acute neuroprotective effects of anti-inflammatory drugs in an animal model of SE. Here we examined whether treatment of SE with anti-inflammatory agents would modify the evolution of post-SE chronic epilepsy.

Methods: SE was induced by LiCl and pilocarpine in male Wistar rats at postnatal day 21. One hour prior to SE induction, animals in the first group were injected with vehicle, while those in a second group received a single intraperitoneal injection of the combination of two anti-inflammatory drugs: CAY10404 (10 mg/kg; a COX-2 inhibitor) and human recombinant interleukin-1 receptor antagonist (hrIL-1ra; 100 mg/kg). Animals in a third group received injection of the same drug combination and treatment continued for 10 days. Four months after SE, animals were subjected to a continuous EEG and video monitoring for a period of 3 weeks for the purpose of acquisition and analysis of spontaneous recurrent seizures. At the end of monitoring, animals were euthanized and brains were processed for the analysis of mossy fiber sprouting using Timm staining, using a semi-quantitative scale (0-4 scale).

Results: Four months after SE, the incidence of spontaneous seizures were observed in 5 of 7 vehicle-treated rats, 7 of 9 rats with single drug injection, and in 4 of 7 animals with 10-day treatment regimen ($p>0.05$ Across all groups). Protracted anti-inflammatory drug treatment reduced seizure frequency among animals with spontaneous seizures. Over three weeks of monitoring, vehicle-treated rats exhibited minimal-maximal-median seizures of 1-18-3; those which received a single injection - 2-13-3; and animals with repeated injections - 2-4-2 ($p< 0.05$ 10 days of drug treatment vs. two other groups). The analysis of mossy fiber sprouting showed moderate synaptic reorganization in vehicle-treated rats as well as in animals treated with a single injection of anti-inflammatory drugs (Timm scores 1.35±0.17 and 1.48±0.08, respectively). There was a statistically significant decrease in mossy fiber sprouting in the animals treated with anti-inflammatory drugs for 10 days (Timm score 0.94±0.08; $p<0.05$ vs. each of two other groups).

Conclusions: Protracted pharmacological blockade of interleukin-1â and COX-2 exerted disease-modifying effect in an animal model of post-SE epilepsy. These results support the notion that epilepsy patients may benefit from the introduction of anti-inflammatory agents in their treatment scheme.

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1.022

EPILEPTIFORM ACTIVITY IN THE ISOLATED GUINEA PIG BRAIN TRIGGERS INCREASED EXPRESSION OF IL-1BETA AND BLOOD-BRAIN BARRIER DAMAGE

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Rationale: Experimental and clinical evidence suggest that brain inflammation is involved in the pathogenesis of seizures. Inflammatory reactions occur in brain during the epileptic process; in particular, the pro-inflammatory cytokine interleukin(IL)-1beta is rapidly synthesized in rodent brain during seizures, and it is increased in epileptogenic tissue of drug resistant epilepsy patients. IL-1beta contributes to neuronal injury and the development of epilepsy. This cytokine was shown to compromise blood-brain barrier (BBB) integrity, which in turn may contribute to glial cell dysfunction and hyperexcitability. The aim of this study was to investigate parenchymal brain inflammation and BBB damage, after pharmacological induction of epileptiform activity in the vitro isolated guinea pig brain preparation. This approach allows to exclude any systemic or blood cells contribution to the effects of seizures and their consequences.

Methods: Ictal activity was evoked by three-min infusion in the basilar artery of the GABA-A receptor antagonist bicuculline methiodide (50 μM in artificial CSF). Epileptiform activity was recorded by simultaneous electrophysiological recordings in CA1 area of both hemispheres. Brain inflammation was evaluated by immunohistochemical detection of IL-1beta; BBB integrity was assessed in adjacent sections by detection of parenchymal extravasation of FITC-albumin artificially infused into the isolated brain after seizure induction.

Results: Epileptiform activity induced by bicuculine lasted for 2 h (total time in seizures was ~30 min). Immunohistochemical analysis at the end of seizures revealed a significant expression of IL-1beta in glial cells, exclusively in those areas involved in ictal activity (i.e. limbic cortices). Adjacent slices showed parenchymal extravasation of FITC-albumin in brain areas where inflammation occurs. Control brains maintained in vitro for comparable time without bicuculline infusion, showed no IL-1beta immunoreactivity and only minor FITC-albumin extravasation, as compared to brains with epileptic activity.

Conclusions: Seizure activity induced in vitro evokes IL-1beta expression in glia and concomitant BBB damage. These findings suggest that inflammatory mediators produced by glial cells during seizures are responsible for BBB breakdown observed in in vivo models of epilepsy, in the absence of contributions from peripheral immune cells. This mechanism may contribute to hyperexcitability underlying seizures.

1.023

EXCITATORY EFFECT OF TNF-ALPHA ON RAT HIPPOCAMPAL CA1 PYRAMIDAL NEURONS AFTER NEONATAL SEIZURE-INDUCING HYPOXIA

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Rationale: TNF-alpha is a critical mediator of neuro-inflammation and cellular loss or injury following brain insults, but the neonatal brain responds differently than the adult to pro-inflammatory cytokines. We previously reported increased TNF-alpha in neonatal rat hippocampus several days after hypoxia-induced seizures in the absence of cell loss or salient anatomical injury. In the current study, we aimed to determine if TNF-alpha could be detrimental by altering neuronal physiological activity.

Methods: Long-Evans rat pups were subjected to 5-7% O2 for 15 min at age P10 to induce seizures. Whole-cell patch-clamp recordings were obtained from CA1 pyramidal neurons in acute hippocampal slices at P13 (3 days post-hypoxia). Current-clamp recordings of spontaneous activity were obtained for 10 minutes, TNF-alpha (0.5 ug/ml) was added to the bath, and recordings were continued for 30-40 minutes.

For some cells, voltage-clamp recordings were obtained to examine TNF-alpha effects on intrinsic voltage-dependent currents.

Results: TNF-alpha had little effect on resting membrane potential (RMP) or intrinsic membrane properties of the majority of CA1 pyramidal neurons in slices from control animals, but 2/10 (20%) of cells showed a depolarization of the RMP and increase in spontaneous firing that developed within 10-15 minutes of TNF-alpha application. In contrast, 8/11 (73%) of neurons in hypoxia-treated group exhibited RMP depolarization and increased spontaneous firing in response to TNF-alpha ($p = 0.030$, Fisher's Exact test). No significant differences were observed in RMP between groups prior to TNF-alpha application. Voltage-clamp recordings after TNF-alpha indicated a decrease in depolarization-activated outward currents in neurons from the hypoxia-treated group compared to controls, suggesting that decreased voltage-activated K+ currents could have mediated or contributed to the excitatory response.

Conclusions: Hippocampal CA1 pyramidal neurons exhibited an augmented excitatory response to TNF-alpha after neonatal hypoxia-induced seizures sub-acutely and at a time when TNF-alpha levels are elevated. This increased excitation could promote repeated seizures after the initial insult, and potentially contribute to AED refractoriness and exacerbate long-term adverse outcomes.

1.024

LOCAL NEUROMETABOLIC COUPLING SURROUNDING A SEIZURE FOCUS IN RAT NEOCORTEX

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Rationale: Epileptic events elicit an increase in neuronal metabolism and an increase in cerebral blood flow (CBF), bringing oxygenated hemoglobin to the activated neurons. Our previous studies have suggested that CBF has a monophonic increase in the focus and biphasic transient decrease in the surround. For the tissue oxygen, seizures induce a transient dip flowed by an increase in the focus and a sustained increase in the surround. The brain energy need is met predominantly through oxygen consumption mediated by the mitochondrial respiratory chain. Whether local oxygen consumption is coupled to the seizure activity in the focus and surround is unknown.

Methods: We induced acute focal seizures in the rat neocortex by 4-aminopyridine (4-AP, 15mM, 0.5 ìl) injection. Local field potential was recorded to identify ictal discharge. Partial pressure of tissue oxygen (pO2) and CBF were measured with one Clark-style polarographic oxygen microelectrode and a laser Doppler flowmetry probe placed close to the oxygen electrode, which located in the focus or surround. Cerebral metabolic oxygen consumption (CMRO2) was calculated from CBF and pO2 measurements using Gjedde's equation (2005).

Results: The total of 127 seizures was recorded from 11 rats. CMRO2 increased to a maximum of 14.701 ± 3.794 % of baseline (n=9 rats, 54 seizures) in the focus. In the surround region, CMRO2 decreased at a peak of -8.307±2.54 % in 5 of 8 rats (n=43 seizures) and decreased to -5.711± 1.427 % after a transit increase of 6.298±1.279 % in 3 of 8 rats (n=39 seizures).

Conclusions: These results demonstrated a significant increase of oxygen consumption rate in the focus and two types of CMRO2 decrease in the region of surround cortex. This surround oxygen consumption suppression may be responsible for circuit neuronal injury associated with epileptic events

1.025

EARLY LIFE SEIZURES IN THE RAT CAUSE ALTERATIONS OF NMDA RECEPTOR FUNCTION

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Rationale: Hypoxic encephalopathy is the most common cause of neonatal seizures and often leads to the development of epilepsy and cognitive impairment. We have reported changes in NMDAR(NR) function after P10 hypoxic seizures(HS), with NR redox sites reduction leading to enhanced NR eEPSC amplitude (Sanchez et al., J. Neurosci 2000), as well as a reduction in ifenprodil sensitivity in slices removed at 48 hours post HS at P10(Dai and Jensen, AES abstract 1.007, 2004). In this study we hypothesized that early HS at P10 might alter other functional NR eEPSC attributes.

Methods: HS were induced in P10 rat pups by global hypoxia (15 minutes at 4-7% O2). Hippocampal slices were prepared at 1, 24, 48, 96 hrs and 1 week after HS in vivo. NR evoked(e) EPSCs were recorded in CA1 pyramidal neurons at +40. ACSF contained 60 µM picrotoxin and 10 µM NBQX. Ifenprodil (5 µM) or cis-PPDA (2 or 0.8 µM) was used to examine the NR2B or NR2C/D subunit component of NRs. 100 µM DL-AP5 was used to block eEPSCs to confirm their NR identity. NR eEPSC IV curves were fitted with a Woodhull equation to obtain Mg2+ Kd(mM).

Results: Consistent with our prior results, slices removed following HS in vivo showed difference in the ifenprodil blockade. In slices removed at 24 and 48 hrs post HS, there was less effect of ifenprodil(24 hrs, 10.35±4.1%, n=4; 48 hrs, 21.30±6.78%, n=4) compared to controls (24 hrs, 58.2±8.0%, n=4, $p<0.05$; 48 hrs, 71.35±8.1%, n=4, $p<0.05$). In slices removed at 96 hrs or 1 week there was no difference in the ifenprodil blockade (15.54±7.8%, n=5 at 96; 15.97±8.93%, n=5 at 1 week) compared to controls (26.98±6.43%, n=5 at 96, $p>0.05$; 29.47 ± 14.93%, n=4, $p>0.05$ at 1 week). We also examined NR eEPSCs regarding their sensitivity to cis-PPDA. At 48, 96 hrs and 1 week, NR eEPSCs showed differences in the percentage blockade (controls 48 hrs, 32.9±10.3%, n=3; 96 hrs, 48.4±12.3%, n=3; 1 week 72.3±8.43%, n=3). This suggests that NRs at these ages expressed NR2C/D subunits. However, there was no significant cis-PPDA blockade difference between HS and controls (post HS 48 hrs, 37%, n=2; 96 hrs, 44.6±8.83%, n=4, $p>0.05$; 1 week, 70.64±5.76%, n=4, $p>0.05$), implying HS may not influence NR2C/D subunit expression. In contrast, we observed significant difference in Mg2+-sensitivity at 96 hrs post HS, not at 1 week. With Woodhull equation to fit NR eEPSC IV curves, post HS at 96 hrs had larger Mg2+ Kd at 0 mV (12.43±3.45 mM, n=6, $p<0.05$) in comparison to control (6.32±2.41mM, n=5).

Conclusions: Our data suggest that early life HS at P10 cause multiple NR alterations, including decreased NR2B specific antagonist ifenprodil sensitivity, suggestive of a decrease in NR2B levels. In addition, there appears to be a developmental increase in NR2C/D antagonist cis-PPDA sensitivity, but seizures did not alter this maturational phase. Finally, HS decrease Mg2+-sensitivity, mediated specifically by an increased NR3A subunits, given the lack of change in NR2C/D function. In summary, these data justify further evaluation of NMDA subunit expression in the acute period following early HS.

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1.026

ACTIVATION OF INNATE AND ADAPTIVE IMMUNITY AFTER KAINATE-INDUCED STATUS EPILEPTICUS IN TEMPORAL LOBES SENSITIZED BY EARLY LIFE CONVULSIONS

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Rationale: A dysregulated innate immune response, peripheral inflammatory cell infiltration and breakdown of the blood-brain barrier have been implicated in the initiation, progression and perpetuation of seizures. To detect and quantify CNS-infiltrating and CNS resident immune cells, we used an unbiased multi-color flow cytometric analysis of inflammatory cells and tested the hypothesis that early-life seizures prime the brain and allow the infiltration of leukocytes, causing exaggerated microglia activation, increased seizure susceptibility and exacerbation of neuronal injury following a "second-hit" kainic acid (KA)-induced status epilepticus (SE).

Methods: Wild-type C57BL/6 mice were subjected to KA-SE on P14 followed by KA-SE on P28 (KA/KA). Controls included mice injected with KA only at P28 (PBS/KA) and mice not experiencing any seizures (PBS/PBS) (n=6/group). Latency to seizure onset after KA-SE was measured and compared between PBS/KA and KA/KA animals. 24 h after KA-SE (or PBS) at P28, temporal lobes containing hippocampus, amygdala and pyriform cortices were harvested from saline perfused animals and CNS mononuclear cells, isolated using enzymatic digestion and Percoll gradients. To detect the presence of CNS-resident microglia and CNS-infiltrating leukocytes, the absolute total percentages, cell numbers and activation status of microglia and infiltrating leukocytes were quantified using multicolor flow cytometry; data were analyzed using FlowJo software.

Results: CNS-resident and infiltrating cells were identified as microglia (CD11b+CD45LOW); CD4+ T cells (CD45HIGH CD3+CD4+); conventional dendritic cells (cDC) (CD45HIGHCD11b+CD11c+) and macrophages (Mö) (CD45HIGHCD11b+CD11c-). Following KA-SE at P28, we detected infiltration of significant number of peripheral leukocytes in the temporal lobes of mice. Moreover, mice with prior experience of KA-SE (KA/KA) had increased percentages and cell numbers of infiltrating dendritic cells and macrophages compared to PBS/KA or PBS/PBS mice. Notably, there were increased numbers of CD4+ and CD8+ T cells in the brains of KA/KA mice compared to PBS/KA or PBS/PBS controls. Mice with prior experience of KA-SE had significantly shorter latency to subsequent seizures compared to controls (1202 sec ± 65 (KA/KA) vs. 1695 sec ± 129 (PBS/KA), n=10, $p<0.02$).

Conclusions: We detected and quantified peripherally derived innate and adaptive immune inflammatory cells following KA-SE. We show significant increases in CNS-infiltrating peripheral inflammatory lymphocytes, macrophages and dendritic cells after KA-SE in the temporal lobes of mature animals sensitized by early-life seizures. In parallel, there was an increase in later seizure susceptibility in animals exposed to early-life convulsions. Our results suggest that recurrent seizures may exacerbate BBB leakage and infiltration of peripheral leukocytes in the brain and potentiate seizures and seizure-induced changes. Priming effects of early-life convulsions may be mediated by involvement of both innate and adaptive immunity.

1.027

INDUCTION AND EXPRESSION OF MIR-146A, AN INFLAMMATION ASSOCIATED MICRORNA, IN EXPERIMENTAL AND HUMAN EPILEPSY AND IN CULTURED HUMAN ASTROCYTES

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Rationale: Increasing evidence supports the involvement of inflammatory and immune processes in temporal lobe epilepsy. MicroRNAs represent small regulatory RNA molecules that have been shown to act as negative regulators of gene expression controlling different biological processes, including immune-system homeostasis and function.

Methods: We investigated the expression and cellular distribution of micro RNA-146a (miR-146a) in a rat model of temporal lobe epilepsy as well as in human temporal lobe epilepsy. MiR-146a analysis in rat hippocampus was performed by PCR and immunocytochemistry at 1 week and 3-4 months after induction of status epilepticus. Primary human cultures of astrocytes and glioma cell lines were used to study the regulation of miR-146a by inflammatory mediators.

Results: Prominent up-regulation of miR-146a activation was evident at 1 week after status epilepticus and persisted in the chronic phase. The miR-146a expression was confirmed to be present in neurons and reactive astrocytes. In human temporal lobe epilepsy with hippocampal sclerosis, increased astroglial expression of miR-146a was observed mainly in regions where neuronal cell loss and reactive gliosis occurred. Increased glial and neuronal expression was also detected in specimens of focal cortical dysplasia. In human cultured astrocytes, as well as in the U373 human glioma cell line, miR-146a was induced by the pro-inflammatory cytokine interleukin-1â.

Conclusions: The expression of miR-146a in reactive astrocytes supports the possible involvement of microRNAs in the modulation of the astroglial inflammatory response occurring in temporal lobe epilepsy and provides a target for future studies aimed at developing strategies against pro-epileptogenic inflammatory signaling.

1.028

EFFECTS OF DEPRESSED K+ CURRENTS CAUSED BY HIGH [K+]O ON THE EPILEPTIFORM BURSTING: A COMPUTATIONAL STUDY

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Rationale: There are different hypotheses concerning the cellular hyper-excitability associated to epileptiform activity. One of them is related to extracellular ionic variations. During the epileptiform bursting, it is observed an increase of [K+]o (extracellular potassium concentration) and a decrease of [Ca2+]o (extracellular calcium concentration), pointing out the participation of this nonsynaptic mechanism in this abnormal oscillatory pattern. These ionic variations

raise the neuronal excitability. However, it is unclear how these variations could influence the transition to an epileptiform bursting within the ictal phase.

Methods: To better understand the neuronal epileptiform bursting pattern within the ictal phase, the experimental conditions of high [K+]o (8.0 mM/l) and zero [Ca2+]o were replicated in a mathematical model. This results in an extended Golomb model of the CA1 region of the hippocampus. We added important regulatory mechanisms of ion concentration as Na+/K+ pump, ion diffusion and glial buffering. Within these conditions, it was possible to simulate the intracellular membrane potential and to reproduce computationally the epileptiform bursting typically recorded in experiments of rat hippocampal slices exposed to high K+ and zero Ca2+ solution.

Results: We analyzed effects of the depressed potassium currents caused by high [K+]o on the neuronal electrical activity. The model simulations indicated that the system loses its stability at a high [K+]o, transiting to an elevated state of neuronal excitability. In the initial stage, the increase of [K+]o creates favorable conditions to trigger the epileptiform bursting. It happens due to the depression of the potassium leak current that provokes an unbalance between the currents responsible for the cellular resting state. During the neuronal activity, the level of excitability is maintained by a continuous growth of [K+]o that depresses voltage-dependent K+ currents in a positive feedback way. Herewith, the depression of voltage-dependent K+ currents impairs the process of membrane repolarization. At the last stage, with the depression of K+ currents, the Na+/K+ pump plays a key role in the end of epileptiform bursting.

Conclusions: Due to the complex neuronal behavior, mathematical models with biological plausibility have yielded considerable insights into how the cellular mechanisms produce abnormal oscillatory patterns. Using a mathematical model of hippocampal region CA1, computational simulations reproduced seizure-like discharges. Based on experimental evidences that still need theoretical explanations, this work suggests how a high [K+]o may raise the cellular excitability and participate in the beginning and continuation of epileptiform bursting.

1.029

REGIONAL DIFFERENCES IN ARC/ARG 3.1 PROTEIN EXPRESSION IN THE IMMATURE BRAIN INDUCED BY SEIZURES

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Rationale: Activity-regulated cytoskeletal associated protein (Arc/Arg 3.1) is an immediate-early gene that is rapidly induced by neuronal activity. Arc/Arg3.1 is known to be required for long-lasting forms of synaptic plasticity, learning and memory consolidation. It has been demonstrated that Arc/Arg3.1 selectively regulates trafficking of AMPA-type glutamate receptors (AMPARs) in neurons by accelerating endocytosis and reducing surface expression of GluR2 and GluR3 subunits. We have previously shown that AMPA receptor trafficking is critical to enhanced network excitability following early life hypoxia-induced seizures (HS) in a rat model of neonatal seizures. We hypothesized that Arc/Arg 3.1 activation may be upstream of AMPA trafficking, which occurs between 1-24 hours after seizures. In the present study we evaluated the temporal and spatial pattern of Arc/Arg 3.1 expression in postnatal day (P)10 rats in which seizures were induced either by hypoxia or by pentylenetetrazol (PTZ).

Methods: Seizures were induced in male Long Evans rats at P10 either by exposure to graded global hypoxia (15 min to min of 4%O2) (n=4) or PTZ dose (80 mg/kg i.p.) (n=4). Untreated littermates were used as controls (n=2). Rat pups were perfused 2, 4 or 6 hours after seizure onset. 20 μM sections were cut from fixed brains and immunostained with Arc/Arg 3.1 antibody (sc-15325, Santa Cruz Biotechnology).

Results: Minimal baseline staining of Arc/Arg 3.1 was seen in the cortex and hippocampus in the P10 controls. As early as 2 hours after PTZ injection, Arc/Arg 3.1. neuronal staining was more intense and widespread in the cortex (cingulate cortex, retrosplenial cortex, neocortical layers II-VI and subplate), hippocampus (CA1, CA3 and dentate gyrus), pyriform cortex and hypothalamus (anterior hypothalamic area, arcuate nucleus, dorsomedial and ventromedial). In comparison, at 2 hours after HS, only slight staining was seen in layer II of the cortex, subplate and pyriform. By 4 or 6 hours, immunoreactivity increased and staining was present in the same regions as PTZ-induced seizures. However, hypoxic seizures resulted in a more intense staining in the pyriform cortex, thalamus and hypothalamus (arcuate nucleus, dorsomedial and periventricular).

Conclusions: These results suggest a change in Arc/Arg3.1 expression induced by seizures in the immature brain. Further studies are required to understand the molecular pathway that relates Arc/Arg3.1 protein with AMPARs.

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1.030

LONG-TERM MODULATION OF THE SYNAPTIC PLASTICITY IN SOMATOSENSORY AREA OF NEOCORTEX BY RECURRENT FLUROTHYL SEIZURES INDUCED EARLY IN LIFE

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Rationale: Seizures in the immature brain can lead to the long-term alteration of excitatory-inhibitory balance which may result in a number of behavioral abnormalities in adulthood. In our recent report, we show that recurrent seizures induced in rats during early development affects the seizure susceptibility of somatosensory cortex. Also we showed a significant alteration of inhibitory and NMDA dependent excitatory postsynaptic transmission in pyramidal cells of Layer 2/3 of somatosensory neocortex. The purpose of the present study was to examine if the flurothyl seizures induced in young animals affect synaptic plasticity in the somatosensory region of neocortex later in life.

Methods: Thirty Sprague-Dawley rats were used throughout studies. The volatile agent flurothyl was used to induce seizures. Fifteen rats were exposed to flurothyl five times per day for 15 days beginning at postnatal day (P) 1. Control rats (n=15) were placed in the chamber for equivalent periods of time as the flurothyl-treated rats but were not exposed to flurothyl. Experiments were performed at the postnatal age of 60 to 80. Recordings were made in coronal cortical slices. Extracellular recording electrodes were placed in the L2/3 of the somatosensory neocortex, stimulating electrodes were positioned in the same column but in L5/6. Potentiation of evoked field potentials was induced using prime burst protocol.

Results: We show that the conditioning stimulation of L5/6 area of somatosensory cortex induce short-term increase in evoked field

potentials in L2/3 area in slices from control rats. This increase lasted no more than twenty minutes. Adding the blocker of inhibitory synaptic transmission gabazine in the recording pipette solution increased the magnitude of potentiation in response to the second and third conditioning stimuli in control slices. However, the potentiation observed in control slices in the presence of gabazine rapidly declined after the third conditioning stimuli with only a 10% increase of field potential amplitudes observed after 40 minutes. In slices from flurothyl exposed rats we observed prolonged increase in amplitude of field potentials in response to the conditioning stimulation. In the condition when inhibitory synaptic transmission was blocked conditioning stimulation evoked increases magnitude of field potential in slices from flurothyl treated rats to the same value as for control slices. However, the duration of potentiation significantly increased comparatively to control slices.

Conclusions: Our findings demonstrate that seizures induced by flurothyl early in development have a long-term effect on the plasticity of somatosensory cortex (Sponsored by NIH NINDS grant numbers: NS041595).

1.031

RAPID LOSS OF DENDRITIC HCN CHANNEL EXPRESSION FOLLOWING STATUS EPILEPTICUS

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Rationale: Hyperpolarization-activated cyclic nucleotide-gated (HCN) ion channels are voltage-gated ion channels expressed in hippocampal and neocortical pyramidal neuron dendrites that diminish excitability. We and others have demonstrated the loss of expression and downregulation of gating of HCN channels during the development of epilepsy following status epilepticus (SE): the density of I_h, the current mediated by HCN channels, declined to 40-50% of control levels by 1 wk after pilocarpine-induced SE, along with an ~50% loss of HCN1 protein expression (Jung et al., 2007; 2010). Both remained decreased at 3-5 wk in chronically epileptic animals, while loss of HCN1 mRNA expression began at 3 d post-SE and persisted at 30 d (Marcelin et al., 2009). In the present study, we sought to characterize the acute timecourse of the post-SE decrease in I_h, and its molecular correlates.

Methods: Dendritic cell-attached patch clamp recordings in CA1 hippocampal neurons were obtained in brain slices from rats after pilocarpine-induced SE, along with Western blotting for HCN1 protein, and real-time RT-PCR for HCN1 mRNA.

Results: At 1 h post-SE, I_h was significantly decreased compared to control levels (all values reported as % of control), with I_h at maximal activation reduced to 50 ± 2.0 %, $p<.01$ vs. control), while HCN1 protein (95 ± 3.0 %) and mRNA levels (98 ± 11 %) were unchanged. At 1 d post-SE, I_h declined further (27 ± 1.0 %, $p<.05$ vs. 1 hr levels), and HCN1 protein levels had also declined to 54 ± 10 % ($p<.01$), while HCN1 mRNA levels remained unchanged (110 ± 22%). We then replicated the rapid loss of I_h with an in vitro model of SE. Hippocampal slices from naïve rats were perfused with solution containing 0 Mg^{2+}, 50 ìM bicuculline, and stimulation (5 stimuli at 50 Hz) of the perforant path to CA1 every two minutes for 1 hr, which produced electrographic seizure-like events recorded extracellularly in str. pyramidale. After 1 hr of this in vitro SE, dendritic I_h declined to 56 ± 13% of control ($p<.05$) , similar to that seen with in vivo SE.

Conclusions: These results demonstrate rapid loss of dendritic I_h, occurring within 1 hr post-SE, elicited by SE both in vivo and in vitro, and persisting during chronic epilepsy. Following in vivo SE, there is a delayed loss of HCN1 protein expression beginning at 1 day, while loss of HCN1 transcription is not seen until 3 days post-SE. This shows that dendritic HCN channelopathy begins at the earliest timepoints following SE, and that the early loss of I_h and HCN1 protein expression precedes the downregulation of HCN1 gene transcription, thus may be due to post-translational mechanisms.

1.032

REDUCED EXCITABILITY OF GABAERGIC INTERNEURONS IN THE RETICULAR NUCLEUS OF THE THALAMUS AND SLEEP IMPAIRMENT IN A MOUSE MODEL OF SEVERE MYOCLONIC EPILEPSY OF INFANCY

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Rationale: The reticular nucleus of the thalamus (RNT) lies between the cerebral cortex and the thalamus. It is populated entirely by GABAergic neurons that modulate the bi-directional flow of information between the thalamus and the cortex and are essential for normal sleep rhythms. Severe Myoclonic Epilepsy of Infancy (SMEI or Dravet Syndrome) is a malignant childhood epilepsy syndrome caused by heterozygous loss-of-function mutations in SCN1A, the gene encoding the Type-I brain Na+ channel, NaV1.1. GABAergic hippocampal interneurons and cerebellar Purkinje cells of Scn1a heterozygotes, our mouse model of SMEI, have greatly reduced NaV currents (47.0 ± 7.0 % and 60 ± 6.0 % of wild-type (WT), respectively). Firing ability of these neurons is remarkedbly reduced, suggesting that their dysfunction plays a key role in hyperexcitability, epilepsy and ataxia observed in SMEI. In this study, we examined changes in whole cell sodium current and excitability of RNT GABAergic neurons as well as their associated effects on sleep in our mouse model of SMEI.

Methods: Whole-cell voltage and current clamp recordings were obtained from acutely dissociated RNT neurons using an Axopatch 200B amplifier and HEKA Pulse software.

Referential digital video-EEG and bipolar EMG recordings were obtained from freely moving mice using thin platinum wire EEG and EMG electrodes on a Telefactor system during wake and sleep.

Results: GABAergic RNT neurons had moderately reduced whole-cell NaV current (78 ± 6.2 % of WT). Rebound bursts of activity following hyperpolarization are characteristic of RNT GABAergic neurons in WT mice. Current clamp experiments on RNT GABAergic neurons from SMEI mice revealed reduced firing during rebound from hyperpolarization (4.0 ± 1.0 action potentials for SMEI vs. 8.5 ± 1.0 for WT in the first 500 ms of rebound), suggesting that the reduced NaV current causes reduced cell excitability. Burst firing by RNT neurons plays a key role in the generation and regulation of slow-wave EEG patterns in sleep. Sleep disturbances are very common in patients with SMEI and other epilepsies. To test whether impaired excitability of the RNT neurons is accompanied by altered sleep architecture in SMEI mice, wake and sleep Video-EEG-EMG activity was recorded from WT and SMEI mice. SMEI mice exhibited normal EEG patterns when awake. However, during sleep, EEG activity was abnormal. Numerous interictal spikes were observed, 100 % occurring during Non-Rapid-Eye-Movement (NREM) sleep. None occurred during Rapid-Eye-Movement (REM) sleep. In addition, SMEI mice exhibited 2.3-fold more brief (< 4s) arousals from sleep than WT. Power spectral analysis revealed that SMEI mice have reduced EEG activity during NREM sleep (50 ± 6 % of WT).

Conclusions: Although sleep disorders in epilepsy have been attributed to anti-epileptic drugs, our results suggest that impairment of NaV currents and excitability of RNT GABAergic neurons may lead directly to sleep disturbance in SMEI that is independent of drug treatment.

1.033

ALTERATIONS IN THALAMIC GABAERGIC SIGNALING IN A MOUSE MODEL OF ANGELMAN SYNDROME

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Rationale: Angelman syndrome (AS) is a neurogenetic disorder associated with profound intellectual disability, speech impairment, movement and balance disorder, a unique behavioral profile, sleep disturbances, and refractory epilepsy. AS results from a neuronal deficiency of functional UBE3A (also known as E6-AP), an E3 ubiquitin ligase encoded by the UBE3A gene. UBE3A is imprinted in neurons, such that expression is nearly exclusively from the maternal chromosome. The seizure types, sleep disturbances, and EEG changes seen in AS individuals suggest that dysfunction of thalamocortical circuitry plays a prominent role in the phenotype. In maternal Ube3a knockout (AS) mice, we have recently shown that Ube3a expression is imprinted in reticular nucleus and ventrobasal nucleus neurons of the thalamus. To begin to understand the role of Ube3a in regulating thalamocortical circuitry function, we evaluated GABA-A receptor (GABAR) expression and function in AS and WT mice. GABARs are pentameric receptors composed primarily of a combination of á, â and either a ã or ä subunits selected from six á, three â, one ã, and three ä subunit subtypes. The distribution of specific subtypes is highly brain region and cell type specific, and varies during development and in certain disease states. The presence of a specific subunit subtype confers different pharmacological and physiological properties to receptor isoforms.

Methods: In this study, we used a combination of whole cell patch-clamp recordings of acutely prepared thalamic slices and immunoblotting of thalamic homogenates from (P8-28) AS and WT mice to investigate potential alterations in GABAergic signaling.

Results: Over the age range studied, we discovered alterations in the normal developmental profile of spontaneous GABAR-mediated transmission. Further, we measured a trend towards increased tonic current in AS mice compared to wild types, particularly in animals older than P17. This tonic current showed a greater response to the ä subunit subtype-preferring agonist DS2. Consistent with this finding, we detected an upregulation of á4 and ä receptor subunit subtypes in the thalamus of P17-28 AS mice relative to WT littermates (but not at earlier ages).

Conclusions: Our findings suggest that alterations in thalamic GABAR subunit expression, including upregulation of extrasynaptic receptors over the course of early development, contribute to thalamocortical dysfunction in AS. These findings may help to inform the development of new treatments to control seizures and improve the developmental outcome in this devastating disorder.

1.034

INCREASED CARDIAC ARRHYTHMOGENIC POTENTIAL IN A MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: Sudden unexpected death in epilepsy (SUDEP) is a devastating complication of drug-resistant epilepsy. Several mechanisms may contribute to SUDEP including sudden cardiac death. We have previously found decreased Kv4 potassium channel levels in the myocardium of epileptic rats. In this study we sought to determine whether there was an associated alteration in sympathetic drive and in myocardial excitability, thereby posing a risk for sudden death in this model. Indeed, previous work by others has shown that in primary cardiac pathology, alteration in myocardial Kv4 channels is associated with action potential prolongation and lethal arrhythmia.

Methods: Surface electrocardiograms (EKG) were obtained in sham and piloparpine-induced epileptic rats. Heart rates (HR), PR, QRS and QTc intervals were measured (n=15/group). Ex vivo optical mapping of the myocardial action potential was performed in a subset of animals (n=2/group). Conduction velocity, action potential duration and the presence of induced ectopic beats were evaluated. Atenolol (10mg/kg/day, i.p.) and vehicle were given to a subgroup of sham and epileptic rats for 1wk (n=4/group). Pre- and post-treatment EKG was obtained and HR, PR, QRS and QTc intervals were measured.

Results: Epileptic rats exhibited increased resting HR compared with sham (273±16.5 vs. 238±3.6 beats/min, $p<0.05$). Compared with sham, epileptic rats also exhibited prolonged QRS (89±5 vs. 73±5 msec, $p<0,05$) and QTc (336±11 vs. 289±11 msec, $p<0.01$) intervals. Optical mapping showed slower conduction velocity (0.44m/s vs. 0.74m/s) in hearts from epileptic compared to sham rats. Stimulation induced ectopic beats in the epileptic but not in the sham heart preparation. In the epileptic rats, atenolol did not significantly lower HR (333±42 vs. 275±39.1 beats/min, pre vs. post atenolol, $p=0.08$), but the QTc was normalized (298±8 vs. 269±7 msec, $p<0.05$).

Conclusions: Our findings suggest that there are alterations in the QTc and arrhythmogenicity in the myocardium from epileptic compared to control animals. While these studies reveal that the changes in the QTc are reversed with atenolol treatment, future studies will evaluate whether this treatment also reverses the changes in myocardial Kv4 channels and abolishes the increased myocardial arrhythmogenicity in this model.

1.035

AGE- AND TIME-DEPENDENT EXPRESSION OF CD74 AFTER KAINIC ACID-INDUCED STATUS EPILEPTICUS

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Rationale: In order to identify time dependent physiological changes underlying epileptogenesis, we have previously investigated time-course of hippocampal gene expression profiles of postnatal day (P)15 and P30 rats after kainic acid-induced status epilepticus (SE) using high-density oligonucleotide arrays. We selected for differentially regulated genes (P30/P15) by capitalizing on age-dependent

physiological responses to KA; KA-SE causes hippocampal neurodegeneration and development of a chronic epileptic state in mature rats (P30), while KA causes neither cell death nor chronic spontaneous seizures in younger animals prior to P21. Genes associated with the mitogen activated protein kinase (MAPK) pathways and inflammation related genes were among the most significantly regulated after KA-SE. Gene expressions were more robust and more sustained in P30 compared to P15. One gene that belonged to both MAPK and inflammation pathway and that displayed a particularly striking gene expression profile after KA-SE, exhibiting an exponentially increasing trend near 240h only in P30 animals was CD74. We performed immunohistochemistry to verify our microarray data and to localize CD74 expression in P15 and P30 rat brains and also in surgically resected cortices from patients with intractable childhood epilepsy.

Methods: Long Evans rats were injected with KA at P15 (3 mg/kg, i.p.) or at P30 (10mg/kg). Control littermates were injected with PBS. Animals that showed generalized convulsions for at least one hour were included in the study and perfused at 24h and 240h (n=3/group/time point). Cortices were from two patients (ages 6 and 12 months) who underwent hemispherectomy for drug-resistant multiple daily seizures. Immunohistochemistry was performed using anti-rat and anti-human CD74 antibodies (Sata Cruz).

Results: In parallel to microarray data, prominent CD74 expressing cells were detected within the hippocampus only in P30 rats at 240h. In addition, intensely CD74+ cells of glia morphology were symmetrically present surrounding white matter tracts including internal capsule, fornix, and anterior commissure and within reuniens thalamic nucleus. Widespread CD74+ cells were detected in both white matter and gray matter of resected cortices. They have morphology of both neurons and glia.

Conclusions: CD74 immunohistochemistry validated our microarray time-dependent expression data of CD74. The presence of cells expressing CD74 was specifically prominent in P30 KA rats at 240h in agreement with the exponential increase in CD74 mRNA noted at 240h after KA in P30 hippocampus. Also, we observed a distinct path of activation for CD74, beginning around the internal capsule and ending near the anterior commissure. CD 74 is a receptor for macrophage migration inhibitory factor (MIF), a proinflammatory cytokine. Binding of MIF to CD74 is required to activate MIF-mediated signal transduction pathways. Delayed activation of CD 74 after KA-SE in adult animals suggests that CD74 protein may play a functional role to regulate seizure-induced inflammation and immune response.

1.036

THE INFLAMMATORY CHEMOKINE CXCL10 FACILITATES LONG-TERM POTENTIATION (LTP) IN THE HIPPOCAMPUS

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Rationale: Clinical observations and experimental studies suggest that central nervous system (CNS) inflammation plays a role in the pathogenesis of epileptic seizures and status epilepticus. For the majority of inflammatory mediators, there is insufficient data so far regarding their effect on epileptogenesis. The chemokine CXCL10, acting via its receptor CXCR3, is involved in the pathophysiological course of several neuroinflammatory conditions (such as viral encephalitis), as well as in neurodegenerative disease associated with an inflammatory component. Most of these conditions are also associated with an increased incidence of seizures or epilepsy. CXCR3 is expressed by resident CNS cells such as microglia and astrocytes, as well as hippocampal and neocortical pyramidal cell. Neuronal CXCR3 receptor activation induces increase of intracellular calcium concentration and depolarization, suggesting that it may contribute to hyperexcitability in inflammatory conditions. The aim of this study was to test the hypothesis that CXCL10, via its receptor CXCR3, increases excitability of a synaptic connection which is part of the mesial temporal network.

Methods: Hippocampal slices were prepared from wild type (WT) mice, and transgenic CXCR3 knock-out (KO) mice, respectively. Field excitatory postsynaptic potentials (fEPSP) were elicited by Schaffer collateral stimulation and recorded in the CA1 region. Long-term potentiation (LTP) was induced by tetanic stimulation (10 trains of 4 pulses at 100 Hz, 200 ms apart). LTP was operationally defined as the mean change in fEPSP amplitude for five intensity stimuli applied beginning 30 min after tetanic stimulation, compared with the mean response to five test pulses given immediately before the stimulation. CXCL10 (100 nmol) was applied to the bath solution 8-12 minutes before tetanic stimulation in a subset of experiments. LTP with and without CXCL10 was compared in pairs of slices taken from the same animal. Data was tested for statistical significance using t-test for paired samples. The significance level was set at $p<0.05$.

Results: In slices prepared from WT mice (n=8), LTP induced a 1.29 ± 0.12 fold increase in fEPSP amplitude. In the presence of CXCL10, LTP induced a 2.04 ± 0.20 fold increase of fEPSP amplitude, which was significantly higher than without CXCL10 ($p=0.006$). In slices from CXCR3 KO mice (n=9), there was no significant difference between fEPSP amplitudes with and without CXCL10 (1.77 ± 0.15 versus 1.44 ± 0.08, $p=0.074$).

Conclusions: Presence of CXCL10 facilitates LTP in the hippocampus of WT mice, whereas it has no significant effect in transgenic mice with knocked-out CXCR3 receptor. Our results suggest that (1) the inflammatory cytokine CXCL10 enhances excitability and acitvity-dependent plasticity in the hippocampus, and that (2) this effect is mediated by its G-protein coupled receptor, CXCR3. CXCL10 may play a role in epileptogenicity associated with inflammatory conditions such as viral encephalitis.

IMAGE: images/906915_A.jpg

1.037

PREDICTING EPILEPTOGENESIS DURING THE LATENT PERIOD AFTER STATUS EPILEPTICUS ON THE BASIS OF DEPRESSION SYMPTOMS DETECTED VIA BEHAVIORAL TESTS

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Rationale: The objective of this study was to find out if comorbidities of Epilepsy such as depression can be detected in the latent period of the rodent model of epilepsy.

Methods: To test for depression in the latent period of post status rodents, 39 Wistar rats were injected systemically with PILO. In the two following weeks of the latent period (before the rats developed chronic seizures), they were tested for depression with two behavioral tests. These tests were the forced swimming test (FST) which was administered for a duration of 5 minutes and the saccharin taste

preference test (STPT), which measures anhedonia- a symptom of depression. Behavioral tests were statistically analyzed. Rats were subjected to 24 hour video-monitoring for 4 months to detect which of them developed recurrent spontaneous seizures and which not. The analysis of behavioral results and video-monitoring were performed blindly by different people. The results were open only after the completion of the analysis.

Results: Out of the 39 rats used, 17 developed seizures eventually, 15 did not, and 7 had complications after the PILO injection and were discontinued from further study. The group of rats that later developed (SZ-group) and the group of rats that did not develop epilepsy (nSZ-group) responded differently on both behavioral tests. There were no significant differences between the nSZ-group and the naïve group in both behavioral tests. On average rats from the SZ-group swam longer (4:17+- 0:27 minutes), than the naive and nSZ-group (respectively 3:38 +-0:26, and 2:43+-0:47 minutes) out of 5 minutes ($p<0.0001$). On the other hand, SZ-group did show signs of anhedonia in the STPT, by having less preference for saccharin during the latent period than the naive rats. The ratio of saccharine/water consumed by the SZ-group rats was much lower (1,8+-1.6) than in naive and nSZ-group rats (3.6+-1.5 and 3.5+-2.5 respectively) ($p<0.01$).

Conclusions: Our experiments showed that during the latent period rats that later develop epilepsy responded differently to the behavioral tests that attempt to estimate the depression. The rats that later develop epilepsy do show a sign of depression on the basis of saccharin taste preference test. However, they are hyperactive on the basis of the forced swimming test. These results provide an additional indication for epileptogenesis as a systemic process involving multiple brain functions. Thus, some behavioral tests could be useful for early diagnosis of epileptogenesis.

1.038

RECURRENT SEIZURES SUPPRESS DENDRITIC GROWTH OF DEVELOPING HIPPOCAMPAL PYRAMIDAL CELLS

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Rationale: Neuronal activity is known to play an important role in dendrite development. But the impact abnormal seizure activity has on dendrite growth and maturation has rarely been studied. Previous experiments in our laboratory have shown that when hippocampal slice cultures, taken from mice 4-6 days-old, are grown in media containing bicuculline (100µM) for 1 week, dendritic growth is markedly suppressed. We have also shown that recurrent seizures suppress the molecular maturation of hippocampal glutamatergic synapses in vivo using the flurothyl model. These results motivated us to study how recurrent seizures affect dendritic growth in developmental CA1 hippocampal pyramidal cells in vivo.

Methods: Experiments were performed using Thy1-GFP-M mice obtained from Jackson Laboratory. On postnatal days (P) 7-11, brief (3 min) flurothyl-induced seizures were produced in infant mice. Three seizures were induced daily for 5 days. Sham littermate control mice were handled identically but without exposure of flurothyl. Following treatment, mice were allowed to survive for varying periods of time (1-20 days) before brains were removed for analysis. On P12, 15, 20, 25, 30, brains were fixed and 300µm slices were made. CA1 hippocampal pyramidal cells were confocally imaged and the basilar dendrites reconstructed using Neurolucida.

Results: Under control conditions, the basilar dendrites of CA1 pyramidal neurons grow rapidly during the first 2 postnatal weeks. For instance, between P6 and P15 the average length of the basilar dendrite nearly doubles from 1354 ± 85 µm to 2548 ± 133 µm (SEM). Thereafter, the dendrites continue to grow but at a reduced rate until P25-30. Sholl analysis indicates that as the hippocampal pyramidal cells mature they add branches both near (< 50 µm radial distance) and at a distance (between 50 and 250 µm) from their somas. In mice that experienced recurrent seizures between P7 and 11, the total length of basilar dendrites is reduced 15.8 % (2494 ± 147 versus 2100 ± 124 µm, $P<0.05$) at P25 and the growth is dramatically arrested from P12 (1958 ± 155 µm) to P30 (2058 ± 120 µm). Comparison of Sholl analyses of seizure-treated samples and their controls indicate that shorter dendrites predominate early-in-life (P12- P20) in experimental samples but with further maturation fewer dendrites of all lengths are observed.

Conclusions: These results suggest that the interruption of synaptic maturation and decreases in molecular markers for glutamatergic synapses seen previously in the flurothyl model may be at least in part be due to a reduction in dendritic arborization. Since dendrites undergo rapid growth during early life, recurrent seizure in vivo may retard or even arrest dendritic growth. Our results suggest that developing neural networks employ unique compensatory mechanisms to control chronic network hyperexcitability. Neuronal network abnormalities produced by the morphological changes reported here could be an explanation for the learning and memory deficits observed in numerous models of early-onset epilepsy.

1.039

FOCAL STATUS EPILEPTICUS IN THE SOMATOSENSORY CORTEX ENHANCES INTRINSIC EXCITABILITY AND SYNAPTIC EXCITATION IN THE RETICULAR THALAMIC NUCLEUS

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Rationale: Thalamocortical circuits are key for the generation of both partial and generalized epileptic seizures. GABAergic neurons from the reticular thalamic nucleus (nRt) inhibit thalamocortical relay cells (TCR), regulate thalamocortical transmission, and generate cerebral rhythms including those involved in thalamocortical epilepsies. nRt neurons receive excitatory inputs from both corticothalamic and thalamocortical axons and would thus receive strong excitatory input during focal and generalized seizures. The response of nRt neurons to such input is not well understood and could promote reorganization of thalamocortical circuits in ways that may lead to hyperexcitability. We therefore examined possible functional alterations in nRt neurons following prolonged episodes of acute seizure activity in the somatosensory cortex.

Methods: Focal status epilepticus (SE) was induced in male P22 mice by unilateral application of a 2 mm pledget of Gelfoam, soaked in 100 ìM GABAzine, to the dura over the somatosensory cortex. Resultant focal electrographic epileptiform activity and associated contralateral partial seizures were monitored for two hours. Mice were then re-anesthetized, the incision reopened, the GABAzine pledget removed and the cortex thoroughly washed with sterile saline. The scalp was then re-sutured and animals allowed to recover. 5-7 days later whole-cell patch-clamp recordings of nRt neurons were obtained from in vitro horizontal brain slices using standard techniques in the presence of inhibitory neurotransmission blockers. Extracellular stimuli delivered to the internal capsule via a concentric bipolar electrode were used to evoke excitatory currents (eEPSCs) in nRt cells, mimicking the excitatory input from the cortex or dorsal thalamus.

Results: Two hour episodes of focal SE lead to robust and long-lasting increases in intrinsic excitability and synaptic excitation in nRt neurons. Compared to naïve controls, nRt neurons in post-status animals showed (1) enhanced post-inhibitory rebound of excitation characterized by a 2-fold increased number of rebound action potentials and a 3-fold increased duration of rebound firing; (2) increased amplitude and lowered threshold for EPSCs evoked by minimal stimulation of internal capsular axons.

Conclusions: Neocortical focal SE chronically enhances both intrinsic excitability and synaptic excitation of nRt neurons. The resultant powerful increase in inhibitory drive from nRt onto TCR cells might suppress excitatory feedback from thalamus to cortex. However, because the output of nRt neurons controls oscillations in the thalamocortical circuits, the increased GABAergic transmission from nRt to TCR cells following SE might promote abnormal oscillations in thalamocortical circuits, leading to amplification and enhanced propagation of cortical epileptic activity. Future experiments will be required to determine if the SE-induced alterations in nRt translate into enhanced thalamocortical oscillatory and epileptiform activity.

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1.040

EFFICACY OF FLUPIRTINE TO TREAT HYPOXIA-INDUCED NEONATAL SEIZURES

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Rationale: Hypoxic encephalopathy is the most common cause of neonatal seizures and survivors often experience neurological problems such as epilepsy in later life. First-line drugs such as phenobarbital are poorly effective in treating neonatal seizures and are associated with a number of side effects. Potassium channels play a uniquely important role in controlling excitability in the developing brain due to immaturity of GABAergic inhibition. Our earlier study demonstrated that flupirtine, a potassium channel opener, was more efficacious than diazepam or phenobarbital for the treatment of chemoconvulsant-induced neonatal seizures. In the current study efficacy of flupirtine to inhibit hypoxia-induced neonatal seizures and its effects on early-developmental milestones were evaluated.

Methods: Ten-day old (P10) Sprague-Dawley rats were treated with either vehicle or with 25, 35, 45 or 50 mg/kg flupirtine 15 minutes before they were exposed to hypoxia. Treated rats were scored for behavioral seizure intensity during hypoxia. The behavioral seizures consisted mainly of head shakes and tonic-clonic limb movements. Hypoxia-induced epileptiform discharges in P10 rats have been shown to last up to 7 days and therefore following hypoxia, rats were treated once a day, everyday for one week with the same dose that was initially given to block the induction of seizures. Rat pups were observed everyday and their body weight, body length, eye opening and righting reflex latency were noted from P10 to P21.

Results: Pretreatment with 50mg/kg flupirtine (n=6) effectively blocked hypoxia-induced behavioral seizures. Also, 50mg/kg flupirtine given 15 minutes after rats were exposed to hypoxia (n=4) blocked the occurrence of acute electrographic seizures. However, treatment with 50mg/kg flupirtine once a day, everyday for multiple days was not well tolerated in terms of age appropriate weight gain. Pretreatment with 35 (n=3) or 45 (n=2) mg/kg flupirtine blocked all type of hypoxia-induced seizure activity, whereas, pretreatment with 25 mg/kg flupirtine (n=6) blocked tonic-clonic seizures in all of the treated rats but was effective in blocking head shakes in only 50% of the treated rats. All rats pretreated with vehicle (n=9) developed head shakes and multiple tonic-clonic seizures. Preliminary studies suggest that treatment with 45mg/kg flupirtine (n=2) adversely affects body length and weight gain but do not affect latency to righting reflex and eye opening. Treatment of rats with either 25 (n=2) or 35 (n=2) mg/kg flupirtine does not affect body weight, body length or latency to righting reflex and eye opening.

Conclusions: These results suggest that 35mg/kg flupirtine is an optimal treatment dose for hypoxia-induced neonatal seizures in rats since it effectively blocks seizures without affecting short-term development. Studies are underway to confirm preliminary results and to determine the effects of optimal flupirtine dose on hypoxia-induced acute electrographic seizures as well as on development of spontaneous seizures and cognition later in life.

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1.041

ANTIEPILEPTOGENIC ACTIVITY OF PROGESTERONE IN MICE LACKING PROGESTERONE RECEPTORS

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Rationale: Progesterone (P) is an anticonvulsant hormone. Women with epilepsy are prone to seizures in response to decreased levels of P during perimenstrual periods. P is being evaluated as a treatment for epilepsy, traumatic brain injury and other complex neurological conditions. Preclinical and clinical studies suggest that P may interrupt epileptogenic events. However, the potential disease-modifying effect of P in epileptogenic models is not widely investigated. In this study, we examined the effects of P on the development of hippocampus kindling in female mice. In addition, we determined the role of progesterone receptors (PRs) in P's activity against kindling epileptogenesis utilizing PR knockout (PRKO) mice.

Methods: Female adult WT and PRKO mice received kindling stimulations in the hippocampus at the 125% current intensity that evoked afterdischarges (AD) according to standard techniques until they exhibit stage 5 seizures. P was administered at a dose of 25 mg/kg, SC twice daily for 2 weeks. The morning dose of P was injected 30-min prior to kindling stimulation. The epileptogenesis was evaluated by monitoring the progression of behavioral seizure intensity and electrographic AD duration. The rate of kindling was compared between control and treatment groups during P treatment and drug-free stimulation sessions.

Results: P, at 25 mg/kg, did not affect seizures and sedative/motor effects in fully-kindled mice. P treatment (25 mg/kg, twice daily for 2 weeks) significantly suppressed the rate of development of behavioral kindled seizure activity evoked by a daily hippocampus stimulation in wild-type mice, indicating antiepileptogenic effect. There was a significant increase in the rate of 'rebound' kindling during drug-free stimulation sessions following abrupt discontinuation of P treatment. P's effects on early kindling progression was partially decreased in PR knockout mice, but the overall (~2-fold) delay in the rate of kindling for induction of stage 5 seizures was undiminished in PR knockout mice. Moreover, the acute anticonvulsant effect of P (50 and 100 mg/kg) was undiminished in fully-kindled PR knockout mice.

Conclusions: These studies provide strong evidence that P exerts antiepileptogenic effect in the hippocampus kindling model at doses that do not significantly affect seizure expression and motor

performance, and the PRs appear to play a modulatory role in epileptogenesis in this model. ** Supported by NIH grant NS051398 **

1.042

PATHWAYS OF INTERICTAL SPIKE PROPAGATION ARE DETERMINED BY NETWORK INHIBITION

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Rationale: Interictal spikes (IIS) are highly correlated with the presence of seizures, and this is the basis of their use as biomarker for epilepsy. Unfortunately the mechanisms underlying IIS initiation, propagation and termination, their role in epilepsy, and the basis for correlation with seizures remain uncertain. In this study we used recordings of human epileptic networks, calcium imaging in vitro, and computational modeling to explore one of these questions, namely the origin of the variance in IIS morphology.

Methods: To study the source of IIS variance, we analyzed the initiation and spread of IIS in patients with long standing pharmaco-resistant epilepsy. We used electrocortigraphic data from subdural grids to map the propagation of IIS through cortex by stacking spatial averages of ÄV at all electrodes for each time point. To study the network determinants of IIS propagation, we used calcium imaging to map IIS-like trajectories in chronically epileptic hippocampal organotypic slices. We also used a large-scale computational model of the CA3 region of hippocampus based on Traub and Miles (1991) with added constraints to make the network scale-free. Connectivity between cells was random and decreased with distance . A limited number of hub-cells were strongly connected with other cells.

Results: Even for multiple spikes originating from a single location, IIS had variable onset trajectories. The recruitment of the same cortical areas occurred in a unique sequence for each spike. Calcium imaging also supported the idea that activation of different areas of the network occurred in unique sequences for each spike in individual hippocampal cultures. To test the influence of interneurons on the pattern of network activation during spikes, we blocked GABA-mediated synaptic inhibition, resulting in most of the trajectory variance being removed. We used the computational model of CA3 hippocampal network to simulate and extend these results. With intact inhibition series of locally synchronized activity occurred randomly throughout the network, and was extinguished by GABAergic inhibition. This activity created localized refractory areas, through which subsequent large-scale synchronous activity propagated poorly, influencing future spikes locations and trajectories. After blocking inhibition, local events were no longer quenched, thus every initiation could spread to involve the entire network, and the pathway variance due to local refractory areas was lost.

Conclusions: In networks with intact GABAergic transmission, inhibition is sufficient to quench nascent IIS, leading to formation of local refractory areas. These refractory areas strongly affect propagation trajectories of subsequent IIS leading to high degree of pathway variability. On the other hand in networks with impaired inhibition the amount of quenching is decreased, resulting in low variability. Thus pathway variance could be used as a noninvasive measure of the functional integrity of the inhibitory system.

1.043

FROM RATS TO MEN: A VIRTUAL WATER-MAZE NAVIGATION TASK TO INVESTIGATE COGNITIVE IMPAIRMENTS IN PATIENTS WITH EPILEPSY

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Rationale: Because it is the most readily accessible measure of memory in rodents, spatial performance in navigation tasks is commonly studied in animal models of neurological disorders. The most widely used task is the Morris water-maze (MWM) task, which consists of training rats to find a submerged platform in a pool of opaque water. In this task, the performance of rat models of temporal lobe epilepsy (TLE) is dramatically impaired as compared to controls. This finding parallels the finding that patients with TLE are commonly affected by pronounced episodic memory impairments. For safety and technical concerns, it is particularly challenging to test water maze performance in humans. In an attempt to parallel the research done in rodents, we developed a virtual reality analogue to the MWM.

Methods: The Human WM task was developed using the “Source Engine” (Valve™). This software is widely used to create custom “first person shooting” video-game environments. The virtual WM was presented on a laptop computer. A Play Station 3 Controller (SONY™) was provided. Movements were restricted to forward/back and left/right body motion. Five healthy volunteers participated in the study. The training environment consisted of a rectangular room (768*396 ft, h= 342 ft; 1 ft= 16 pixels) and the water maze environment was a cylindrical arena (576 ft diameter, h= 123 ft) surrounded by multiple visual cues (a tree, a wall and a building). In both environments, the floor was covered with opaque water (h= 22.5 ft) under which a platform (24*24 ft, h= 2.25 ft) was submerged. Five control subjects were first asked to navigate for 10 minutes in the training environment to get accustomed to the procedure. When the subjects stepped on the platform, a red light turned on to denote success. After training, subjects were dropped in the arena and asked to reach the platform as fast as possible. Once the subject reached the platform, he was allowed to observe the environment for 1 minute without moving. After this delay, he was teleported to another location in the maze. This process was repeated 4 times per session for 3 sessions. The day after, the platform was removed without informing the subjects and they were asked to perform the task once more. Repeated measures ANOVA and logistic regressions were performed.

Results: On the first day, there was a significant reduction in latency to reach the platform by session ($p<0.001$ - repeated measures ANOVA). Latency was significantly longer in session 1 than session 3 ($p<0.001$). After adjusting for latency, there was also a significant reduction in swimming distance ($p=0.017$). During the first 30 seconds of the probe test, subjects spent 70% of their time in the platform quadrant.

Conclusions: These preliminary results show a striking parallel to rodent data in the water maze. The task is easy to learn and performance improved within a few trials. This technique will likely be very useful to investigate spatial performance in patients with epilepsy, and can be done while recording electrophysiological activity.

1.044

CONNEXINS IN THE RAT MODEL OF TEMPORAL LOBE EPILEPSY INDUCED BY PILOCARPINE: EXPRESSION AND GAP JUNCTION BLOCKADE

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Rationale: Gap junctions (GJ) are intercellular channels which can be involved in the generation and propagation of epileptic activity (Trends Neurosci 2000; 23[2]: 68-74), and changes in the expression of connexins (Cx) have been described both in animal models of epilepsy and in patients (Epilepsia 2003; 44[12]: 1596-600). The aim of this study was to evaluate the protein and mRNA levels of Cx in the hippocampus of rats submitted to the pilocarpine (PILO) model of temporal lobe epilepsy (TLE). Besides, in order to verify the effects of a GJ blocker (carbenoxolone - CBX) on the epileptiform discharges and to demonstrate the possible involvement of these channels in the status epilepticus (SE), the electrocorticographic (ECoG) activity of rats submitted to the PILO model was evaluated.

Methods: Male Wistar rats were treated with methylscopolamine (s.c., 1 mg/kg) 30 minutes before the PILO injection (i.p., 360 mg/kg). The animals were divided in 3 groups: acute (sacrificed 4 hours after the beginning of SE, n=12), latent (3 days after SE induction, n=14) and chronic (4 months after SE induction, n=15). Their hippocampi were submitted to immunoblotting and real-time PCR protocols for detection of Cx36 and Cx43. To evaluate the effects of CBX on SE, the animals (n=3) were anesthetized and placed in a stereotaxic apparatus to have electrodes implanted in the cortical area A3. After 7 days of recovery, the animals were submitted to the following data acquisition protocol: a) Basal: 30 minutes of recording for adaptation of the animal; b) Methylscopolamine: 30 minutes of recording after the injection; c) PILO/SE: 30 minutes of recording after SE establishment; d) CBX: recording after injection of CBX.

Some intervals of the above recordings were chosen for spectral analysis of frequency and power.

Results: The immunoblotting data revealed a significant increase (41%) in the expression of Cx36 in the hippocampi of animals analysed in the acute phase. However, the PCR data showed a reduction of the Cx36 mRNA levels in the latent and chronic groups (77% and 58%, respectively). The Cx43 electrophoresis indicated the presence of at least 2 isoforms, named P0 (nonphosphorylated) and P1+P2 (phosphorylated isoforms). An increase of the total amount of protein and of the P1+P2 isoforms was observed during the chronic phase (77% and 81%, respectively). The PCR data revealed a significant increase of Cx43 mRNA only in the latent phase. Treatment with CBX produced a marked decrease in the frequency and amplitude of the epileptiform potentials; moreover, the sharp wave complexes periodically changed their morphology, alternating between polyspike complexes or hypersynchronic slow wave groups, usually sinusoidal without the spike component.

Conclusions: The PILO model of TLE appears to induce changes of the expression of Cx in the hippocampus of rats, suggesting an important role for the GJ communication in this pathology. This idea is strengthened by the results obtained with the CBX treatment, which suggested CBX to be an effective compound in the control of SE induced by PILO.

1.045

A PUTATIVE CELLULAR MECHANISM FOR CHILDHOOD ABSENCE EPILEPSY IN PATIENTS WITH CAV3.2 GAIN-OF-FUNCTION MUTATIONS

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Rationale: Mutations of CACNA1H were discovered in patients with childhood absence epilepsy (CAE). In vitro, the mutations increase T-type Ca2+ channel activity by altering trafficking and voltage gating. Yet, the in vivo effects on seizure susceptibility and neural circuit function remain undefined. We created transgenic mice with a full length CACNA1H gene carrying either of two epilepsy-associated mutations (V831M and C456S) and a C-terminal flag tag to characterize their effects on native T-type Ca2+ currents, circuit properties, and seizure risk during postnatal development.

Methods: Spontaneous and induced seizures were measured by EEG and behavior at baseline and following i.p. bicarbonate and quantified as reported (Zhou et al. Nature Medicine 2009). Whole cell patch-clamp of hippocampal subiculum pyramidal neurons was performed in voltage-clamp and current-clamp mode in transverse hippocampal (300 ìm) slices.

Results: T-type Ca2+ currents were recorded by stepping from a holding potential of -100 mV to a set of test potentials. As reported for Cav3.2 cDNA in vitro, T-type Ca2+ currents in transgenic mice displayed a left shifted voltage-dependent activation curve relative to controls (-43±1 vs. -36±1 mV, $p<0.001$). Interestingly, T-type Ca2+ current density increased during the period of postnatal circuit developmental. At P8-10, current density in C456S mutant mice and wild type mice was not significantly different (4.6±0.4 vs. 4.5±0.4 pA/pF). However, by P17-19, current density increased and was magnified increase in mutant (8.0±0.6 vs. 5.6±0.3 pA/pF, $P < 0.01$). By contrast, in P17-19 Cav3.2 knockout neurons, current density remained low 4.6±1.1 pA/pF significantly lower than mutant at P17-19 ($P < 0.05$). The probability of firing in response to a brief (5 ms) EPSC-like stimulus of 500 pA was 100% in C456S (n = 4) compared to only 33% in wild-type (n = 3). A more prolong 1 sec current injection elicited firing at a lower threshold in C456S compared to wild type (27.3± 3.0 vs. 55.6± 8.0 pA, $P < 0.01$). Surprisingly, at P17-19, C456S mutant neurons displayed spontaneous firing at baseline: 86% in C456S mutant (n = 7 cells), but only 14% in wild-type (n = 7 cells), while resting membrane potential was unaffected (-67±1.3 vs. -67.1±0.9 mV, respectively). Hyperventilation triggers cortical spike-wave discharge in CAE patients with Cav3.2 mutations. Sodium bicarbonate injections (to induced a metabolic alkalosis mimicking the respiratory alkalosis; increasing HCO3-/CO2 ratio) epileptiform activity in frontal cortex selectively in C456S mutant mice 75% (12/16) compare to 0% of control littermates (0/12).

Conclusions: The results indicate CAE-associated Cav3.2 mutant increases T-type Ca2+ current during postnatal development to promote spontaneous discharge of pyramidal neurons and suggest childhood absence epilepsy may arise in part from a transient increase of T-type Ca2+ channels during early childhood that increases circuit excitability to promote epileptiform discharge.

1.046

PENTYLENETETRAZOLE-INDUCED SEIZURES CAUSE ACUTE, BUT NOT CHRONIC, MTOR PATHWAY ACTIVATION IN RAT

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Rationale: Activation of the mammalian target of rapamycin (mTOR) pathway has been implicated in contributing to chronic epileptogenesis in multiple models of epilepsy. In addition, seizures themselves can directly cause acute activation of the mTOR pathway. Our previous work showed a biphasic activation of the mTOR pathway in the kainate model of epilepsy, with an initial acute phase of mTOR activation lasting a few hours stimulated immediately by kainate-induced seizure activity and a second, more chronic phase over a few weeks correlating with the process of epileptogenesis and eventual development of spontaneous seizures. In contrast to the kainate model, pentylenetetazole (PTZ) is an antagonist of the gamma-aminobutyric acid (GABAa) receptor that can cause acute seizures in rodents, but does not usually lead to the development of spontaneous epilepsy. In this study, we tested the hypothesis that PTZ-induced seizures cause acute, but not chronic mTOR pathway activation.

Methods: Six-week old SD rats were injected with a single dose of PTZ (75 mg/kg, i.p.). The latency and duration of convulsive seizure activity were observed behaviorally. Rats were then sacrificed at various times intervals (1, 3, 6, and 16 hours, 1, 3 and 7 days, or 3 and 5 weeks) after the onset of seizures. Vehicle-injected rats served as controls. The neocortex and hippocampus were harvested individually at the different time points. Western blot analysis was performed on phospho-S6 (P-S6) and total S6, with the ratio of P-S6 to S6 expression serving as a measure of mTOR pathway activity. In addition, phospho-Akt and total Akt expression was examined as a potential upstream mediator of mTOR activation.

Results: PTZ injection induced acute convulsive seizure activity within a few minutes and caused a corresponding activation of the mTOR pathway, as reflected by an increase in the P-S6 to total S6 ratio. P-S6 expression peaked at 3-6 h and returned to baseline by 16 h after seizure onset in both hippocampus and neocortex. In contrast to the kainate model, there was no secondary chronic increase in P-S6 expression observed over days to weeks following PTZ-induced seizures. Similar to P-S6, phospho-Akt protein expression was upregulated in the first few hours after the onset of PTZ-induced seizures.

Conclusions: PTZ-induced seizures result in acute immediate activation of the mTOR pathway, without a later, more chronic effect on mTOR activity. The acute activation of the mTOR pathway by seizures may be mediated through upstream activation of Akt. In comparison to the kainate model, the lack of a late phase of mTOR activation might account for the absence of epileptogenesis and the development of epilepsy in the PTZ model. Future studies aimed at identifying mechanistic differences in mTOR pathway activation between the PTZ and kainate models may provide important insights into mechanisms of epileptogenesis. Supported by NIH NS056872.

1.047

AN ORGANOTYPIC HIPPOCAMPAL SLICE CULTURE MODEL OF EXCITOTOXIC INJURY INDUCED SPONTANEOUS RECURRENT EPILEPTIFORM DISCHARGES

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Rationale: Stroke has long been recognized as the most common cause of epileptic seizures in adults age 60 and over, accounting for over 35% of new-onset symptomatic cases of epilepsy in the elderly population. Though this association between stroke and epilepsy is well recognized, it is not well understood. Acquired epilepsy (AE) is one of the most common neurological disorders with significant consequences on quality of life. Neuronal insults such as stroke can induce neuronal plasticity changes that lead to epilepsy during the latent period after injury known as epileptogenesis. Various changes in synapses and receptor organization can be seen in epileptic tissue, but very little is known about the molecular mechanisms underlying this condition. To more efficiently study the plasticity changes that occur during epileptogenesis, we have developed a model of spontaneous recurrent epileptiform discharges (seizures) after a stroke-like injury in organotypic hippocampal slice cultures (OHSCs). OHSCs represent an advantageous model to study stroke-induced AE because they maintain neuronal morphology, cellular and anatomical relations, and network connections.

Methods: Our model employs a glutamate injury paradigm that is representative of a stroke-like injury. Treatment protocol consisted of exposure to 3.5 mM glutamate for 35 minutes at DIV 21 followed by removal of glutamate and return to maintenance medium. Cell death was measured using propidium iodide (PI). Electrophysiological techniques consisted of field potential recordings and whole-cell current clamp recordings.

Results: Glutamate injury revealed neuronal loss similar to that seen in other stroke models: compared to controls at 24-h cell death was 60% greater, and at 72-h it was 23% greater in glutamate treated slices. Beyond this time point cell death was not different from control. These data indicate that the initial injury phase is responsible for most of the cell death in OHSCs. The surviving, but injured cells are an ideal substrate for epileptogenesis. Indeed, field potential recordings at DIV 28-31 revealed seizure-like activity in approximately 46% of OHSCs, compared to 7.14% of controls. In addition, intracellular recordings from single CA3 pyramidal cells displayed spontaneous recurrent epileptiform discharges in about half of the glutamate-injured OHSCs, but not in the controls. Further, in field potential recordings, seizure activity was inhibited by the anticonvulsants phenobarbital and phenytoin, but not by ethosuximide.

Conclusions: The morphological changes, electrophysiological characteristics and response to standard anticonvulsant treatment observed in our model is similar to stroke-induced AE in the human condition and in vivo models of epilepsy, making this a simple and powerful model to explore the underlying molecular mechanisms and changes that occur during epileptogenesis.

1.048

PREDICTING CORTICAL NEURON SPIKE PATTERNS: POINT PROCESS MODELING OF AN EPILEPSY COMPUTATIONAL SIMULATION

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Rationale: A neural network simulation using a model with realistic cortical architecture has been previously used to study synchronized bursting dynamics as a seizure representation (1). This model has the interesting property that bursting epochs arise spontaneously and cease at random intervals, making the onset of the seizure-like episodes difficult to predict. Recently, a point process model utilizing single unit recordings from human cortex has been demonstrated to show single

neuron spike prediction abilities (2). We now test a similar point process prediction model on our neocortical simulation using random background inputs mimicking the role of surrounding cortex, with the goal of characterizing the subnetworks which are active in the generation of epileptogenic behavior.

Methods: Point process models were used to fit the spiking probabilities in 10-msec time bins for a neural network simulation of neocortex. This simulation includes several classes of excitatory and inhibitory single-compartment neurons arranged and connected in space in a biophysically realistic fashion (1). The fitting technique was similar to that used by Truccolo et al. (2). Fitting terms corresponding to a given neuron's intrinsic spiking history as well as the extrinsic spiking history of randomly selected neighboring neurons were included. The fitting parameters were determined using the method of maximum likelihood conditioned on the observed spiking history over preceding time epochs of 100-msec in duration.

Results: The point process model has been tested on 10 seconds of spiking data from pyramidal cells in layer II/III of the neural network simulation. Figure 1 displays four pre-spike filter functions used in the point process model. They display large amplitudes at short time scales and taper off of at longer times. Figure 2 displays the resulting conditional probability of firing by conditioning solely on the intrinsic history for a single cell using ten pre-spike filters. Predicting spikes by thresholding over the conditional probability would not produce reliable results as evidenced by the discordance in timing between the peaks of the predictions (blue trace) and the actual spike times of the cell (red dots). Including the extrinsic history from a random subset of ~20 neurons in the vicinity of this cell improves performance.

Conclusions: The point process model has been tested on spike trains from a neural network simulation of epilepsy (1). We find that conditioning solely upon intrinsic spike trains does not provide reliable prediction. We aim to use this model to further delineate in which instances one can reliably perform single unit spike prediction in a spiking model of epilepsy with random inputs.

1. Anderson WS, et al., Studies of stimulus parameters for seizure disruption using neural network simulations. Biol Cybern. 97 (2): 173-194, (2007).

2. Truccolo W, et al., Collective dynamics in human and monkey sensorimotor cortex: predicting single neuron spikes. Nat Neuro. 13 (1): 105 - 111, (2010).

Support: Charles H. Hood Foundation (FA, WSA), NIH-NINDS KNS066099A (WSA)

IMAGE: images/906679_A.jpg

Figure 1. Pre-spike filters applied to both the intrinsic and extrinsic histories of spiking neurons in our neural network simulation. Four filters are exhibited. They comprise sine functions which are stretched out at long times.

IMAGE: images/906679_B.jpg

Figure 2. Conditional probability (blue) shown for a 1100-msec time window, where a single layer II/III pyramidal cell in the center of the neural network simulation shows spiking activity (red). We note that conditioning solely on intrinsic histories (for N = 10 pre-spike filter functions) does not provide reliable prediction in this instance.

1.049

LONG-LASTING CHANGES IN MGLUR MEDIATED LONG TERM DEPRESSION FOLLOWING A SINGLE EPISODE OF EARLY LIFE SEIZURES

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Rationale: Previous research in our lab has indicated that following a single episode of early life seizures (ELS), induced using kainic acid (2 mg/kg) on post-natal day (PND) 7, rats display increased LTD (long term depression), as well as cognitive deficits at PND 60+. These changes occur in the absence of pronounced hippocampal injury (cell loss and synaptic reorganization) and are consistent with molecular alterations at the sub-cellular or synaptic level. We speculate that increased LTD (in conjunction with decreased LTP) may be responsible for the observed learning abnormalities. LTD induction can be mediated by two distinct mechanisms, NMDA receptor (NR) dependent and metabotropic glutamate receptor (mGluR) dependent. The NR dependent and mGluR dependent forms are differentiated by the effectiveness of different chemical and electrical LTD inducing stimulation paradigms. We hypothesize that alterations in LTD following ELS are the result of changes in mGluR dependent LTD. Therefore mGluR dependent LTD induction paradigms were employed to test this hypothesis. We further hypothesize that the expression levels of sub-synaptic machinery associated with LTD will reflect their role as potential mediators of the changes following ELS.

Methods: LTD induction paradigms designed to isolate mGluR dependent LTD were utilized. Specifically, LTD was induced using 900 paired-pulse stimuli at 1Hz with 50-millisecond interpulse interval in the presence of D-APV (50 ìM). LTD was also induced using DHPG (100 ìM) (50 ìM), an mGluR agonist. Potential mediators of the observed changes in mGluR dependent LTD were assessed using semi-quantitative western blot expression assays.

Results: A single episode of neonatal seizures resulted in enhanced mGluR mediated LTD. Field excitatory postsynaptic potentials (fEPSPs) were measured from the stratum radiatum of the CA1 region of adult hippocampal slices in response to stimulation of the Schaffer collateral-commisural pathway. ELS animals displayed enhanced LTD after induction with 900 × 50-millisecond paired pulses at 1Hz, as well as following DHPG wash-in ($p < 0.05$). Expression of activated p90S6K, áCamKII, and âCamKII was significantly ($p < 0.05$) increased. Expression of activated GSK3â and Akt were not altered ($p < 0.05$). Expression of total p90S6K, áCamKII, âCamKII, FMRP, GSK3â, Akt, and STEP were not significantly altered ($p < 0.05$).

Conclusions: ELS results in long-term signaling changes resulting in enhanced mGluR mediated LTD compared to age matched controls. The enhanced LTD is apparent regardless of the induction paradigm (900 × 50-millisecond paired pulses at 1Hz, or DHPG induced). Signaling proteins associated with mGluR LTD were also altered in a consistent fashion, suggesting a mechanisms for the observed changes in LTD, as well as possible targets for therapeutic intervention. We speculate that this altered mGluR dependent LTD may underlie some of the learning abnormalities detected following ELS.

1.050

EFFECTS OF BETA ADRENERGIC ACTIVATION ON THE INTERICTAL AND ICTAL-LIKE ACTIVITY IN VITRO

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Rationale: Quantification of the spatio-temporal neuronal activity patterns underlying electrographic epileptic signatures is critical for decoding these abnormal dynamics. It requires an ability to simultaneously monitor extended tissue areas and the activity of individual cells with high temporal resolution. Presently we lack clear understanding of the mechanisms of these processes and how they are influenced by underlying circuitry or neuromodulatory afferents. The aim of the current study is to investigate the genesis, evolution and beta adrenergic receptor (â-AR) effects on emergent interictal and ictal-like activity in anatomically-distinct rodent brain preparations using concurrent electro-optical toolkit.

Methods: To study epileptiform activity and its neuromodulation by norepinephrine-like agonists, we used transverse hippocampal and visual neocortical rat brain slices (P21-P30). In acute 4-Aminopyridine (4-AP; 50-100µM) seizure model, both structures generated electrographically similar interictal bursts (IBs) and ictal-like events, which were further modulated by â-AR agonist isoproterenol (ISO, 10µM). Concurrent fast voltage-sensitive dye (Di-4ANNEPS and Di-8ANNEPS) imaging (MiCam Ultima-CMOS, 100x100 pixels; 0.5-1KHz) and extracellular or whole-cell recordings were performed. We analyzed sites of IB and ictal-like event origin, duration, velocity of propagation, power spectrum, and local and global synchronization dynamics (Brainvision and Matlab).

Results: Both structures exhibited short duration (70-500msec) IBs and longer ictal-like events in the presence of 4-AP. Application of ISO significantly reduced the duration (hippocampus CA1: from 49 to 20 sec., n=9 slices; visual cortex layers II-III: 132 to 72 sec., n=4 slices) or completely blocked ictal-like events. In hippocampus, most of the IBs originated from dentate gyrus/CA3 border and propagated downstream the tri-synaptic pathway toward CA1 (n=6 slices; 120 IBs). In the VC, 46.7% of IBs originated in layers II/III, 11.5% in layer IV, 9% in layer V, and 25% in layer VI (349 optical bursts; n=6 slices). ISO left IB origin sites unchanged, but instead increased frequency of IBs, and confined the spatial extent of the IB activity in the hippocampus to 30-50% of that seen in 4-AP (measured using spatial activation maps, n=4 slices; 60 IBs). Velocity of IB propagation from the hippocampal CA3 to CA1 area showed a significant decrease (0.3m/s to 0.16m/s; n= 6 slices; 120 IBs). IB inter-event interval durations were more regular in 4-AP (on average 600-800msec), while in 4-AP+ISO this interval was more variable (600-1500ms; n=3 slices, 58 bursts in 4-AP and 123 bursts in 4-AP+ISO).

Conclusions: Anatomically diverse architecture and modulatory inputs play important roles in patterning the spatio-temporal dynamics of epileptiform activity emergence and propagation. The effects of ISO indicate the existence of hyperexcitable, rhythmically irregular, and spatially desynchronized epileptic-like state mediated by â-AR activation.

1.051

DEFICIT OF SMALL-CONDUCTANCE CALCIUM-ACTIVATED SK POTASSIUM CHANNELS IN PILOCARPINE-TREATED EPILEPTIC RATS

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Rationale: Small conductance calcium (Ca2+) activated SK channels are critical regulator of neuronal excitability in hippocampus. Accordingly, these channels are thought to play a key role in controlling neuronal activity in acute models of epilepsy. In this study, we investigate the expression and function of SK channels in the pilocarpine model of mesial temporal lobe epilepsy.

Methods: For this purpose, protein expression was assessed using western blotting assays and gene expression was analyzed using TaqMan-based probes and the quantitative real-time polymerase chain reaction (qPCR) comparative method delta-delta cycle threshold (DDCT) in samples extracted from control and epileptic rats. In addition, the effect of SK channel antagonist UCL1684 and agonist NS309 on CA1 evoked population spikes was studied using extracellualr recordings in hippocampal slices obtained from control and epileptic rats.

Results: Our findings indicate no changes in protein and transcript expression of SK1 channels in chronic epileptic rats. In contrast, a significant down-regulation of SK2 and SK3 channels was detected in tissues obtained from chronic epileptic rats. Real-time quantitative PCR analysis of gene expression revealed that a significant reduction of transcripts for SK2 and SK3 channels occurred as early as 10 days following pilocarpine-induced status epilepticus and persisted during the chronic phase of the model. Moreover, bath application of UCL1684 (100 nM for 15 min) in control and epileptic slices induced a significant increase of the population spike amplitude and number of spikes in the hippocampal CA1 area. This effect was obliterated by co-administration of UCL1684 with SK channel agonist NS309 (1 ìM). Application of NS309 failed to modify population spikes in the CA1 area of slices taken from control and epileptic rats.

Conclusions: These data indicate an abnormal expression of SK channels and a defective function in the pilocarpine model of temporal lobe epilepsy. Accordingly, drugs that enhance the function of SK channels can potentially act as antiepileptic drugs in temporal lobe epilepsy.

1.052

FUNCTIONAL EFFECTS OF LONG-LASTING, SEIZURE-INDUCED ALTERATIONS IN NKCC1 AND KCC2 IN THE DENTATE GYRUS OF KINDLED RATS

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Rationale: [Cl^-] gradients maintained by the electroneutral ion co-transporters NKCC1 and KCC2 determine whether GABA has hyperpolarizing or depolarizing effects in both immature and adult

neurons, thereby influencing $GABA_A$ dependent control of neuronal and network properties contributing to seizures and epilepsy. NKCC1 is an inward directed Na^+-K^+-$2Cl^-$ co-transporter that increases intracellular Cl^-. KCC2 is an outward directed K^+-Cl^- co-transporter that reduces intracellular Cl^- in normal $[K^+]_o$, but reverses transport and imports Cl^- when $[K^+]_o$ increases, as occurs during seizures. Repeated Class V seizures but not partial seizures in kindled rats induce robust long-lasting increases in expression of NKCC1 followed by very modest increases in KCC2 after 100 Class V seizures, a kindling stage associated with emergence of spontaneous seizures (see Sutula et al., meeting abstracts). The goal of this study was to examine effects of the long-lasting seizure-induced increases of NKCC1 and KCC2 on resting membrane potential (RMP), reversal potential of the IPSP (E_{ipsp}), and spike (AP) threshold.

Methods: Sharp electrode current-clamp recordings were obtained in granule cells of the dentate gyrus in hippocampal slices from normal and kindled rats that experienced repeated seizures evoked by perforant path stimulation. Monosynaptic IPSPs were evoked by a stimulus pulse applied near the recording electrode in 20 µM DNQX and 50 µM APV to block glutamate receptors. The peak amplitude of the IPSP was measured during constant DC pulses across a range of current intensities. IPSP amplitude was plotted as a function of the steady state membrane potential to determine the E_{ipsp}. E_{ipsp} was compared in slices obtained from rats that experienced only partial (Class I-IV) seizures, a range of 5-90 secondary generalized (Class V) seizures, and > 100 Class V seizures, a kindling stage associated with spontaneous seizures.

Results: In 3.75 mM $[K^+]_o$, there were no differences in RMP, E_{ipsp}, or AP between control and kindled rats. In 9.75 mM $[K^+]_o$, the E_{ipsp} in slices from normal rats shifted from -73.3 mV to -54.0 mV, but in kindled rats with Class V seizures the E_{ipsp} shifted from -71.3 mV to only -61.4 mV ($p< 0.001$), a difference corresponding to the expected effects of increased NKCC1 expression and reversal of KCC2 regulated Cl^- flux in $[K^+]_o$ = 9.75 mM. There were no differences in E_{ipsp} between normal and kindled rats with only partial seizures, or rats with < or > 100 Class V seizures.

Conclusions: The results are consistent with Cl^- loading from seizure-induced increases in NKCC1 and reversal of Cl^- flux by KCC2 in elevated $[K^+]_o$. While increases in intracellular Cl^- from seizure-induced increases in NKCC1 could contribute to excitatory effects of GABA in chronic epilepsy, the overall functional effects of seizure- induced alterations in co-transporters more likely dampen network excitability during interictal or ictal conditions when $[K^+]_o$ is elevated.

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1.053

ERK AND MTOR PATHWAY INTERACTIONS IN EPILEPSY

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Rationale: The mammalian target of rapamycin (mTOR) and extracellular regulated kinase (ERK) pathways are aberrantly regulated in epilepsy. Interaction between the ERK and mTOR pathways occurs at various upstream and downstream levels and is well-described in tumor biology. For example, activated ERK can phosphorylate tuberous sclerosis complex 2 (TSC2) and S6 in the mTOR pathway. However, the physiological role of ERK and mTOR pathway cross-talk in neurons is not well-understood. Furthermore, while both pathways are activated in some forms of epilepsy, it is unclear if there is ERK and mTOR cross-talk in this context. In the studies presented here we sought to further characterize ERK pathway coupling to mTOR signaling in neurons and in human brain tissue resected for treatment of drug resistant epilepsy.

Methods: HEK293 cells and cortical neurons were transfected with constitutively active MEK1 (caMEK1) copGFP to elicit ERK activation or a copGFP only (control). Activation of ERK and mTOR signaling in these cells was determined using immunohistochemistry (IHC) and western blotting (WB) with antibodies against the phosphorylated forms of ERK (pERK), TSC2 (ERK phosphorylation site S664; pTSC2), and S6 (phosphorylation site S235/236; pS6). Since these pathways are implicated in dendritic remodeling, dendritic morphological analysis of transfected mouse cortical neurons also was performed using Neurolucida software. Human brain tissue sections obtained after resection from epilepsy surgery were stained with these antibodies and IHC was correlated with the neuropathological and clinical history.

Results: IHC and WB showed that activation of ERK correlates with increased levels pTSC2 and pS6 in HEK293 cells (WB: $p<0.001$, n=5) and mouse cortical neurons. Dendritic morphological analyses of cultured neurons with high levels of pERK showed a decrease in the number of dendrites ($p<0.001$, n=5) and dendritic branching ($p<0.001$, n=5) compared to controls expressing copGFP. Furthermore, IHC analysis of brain sections obtained from individuals undergoing epilepsy surgery showed aberrant labeling with pS6, pTSC2 and pERK antibodies in areas of cortical dysplasia.

Conclusions: Our findings suggest that there is ERK and mTOR pathway cross-talk at the level of TSC2 and S6 in neurons under physiologic conditions and in epilepsy. Future studies will elucidate the role of interplay between these two pathways in the CNS and may provide support for targeting both pathways in epilepsy.

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1.054

MECHANISMS OF CORTICAL HIGH-GAMMA ACTIVITY (60-200 HZ) INVESTIGATED WITH COMPUTATIONAL MODELING

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Rationale: Very fast oscillations in LFP and EEG, ranging in frequency between 80 Hz and 250 Hz, have been observed in spatial and temporal patterns corresponding to the epileptogenic zone in patients with epilepsy and in experimental models of epilepsy (Fisher et al., J Clin Neurophysiol, 1992; Traub et al., Epilepsia, 2001). On the other hand,

high-gamma activity (HGA) in overlapping frequencies (~60-200 Hz) have been observed during task-related cortical activation in humans (Crone et al., Prog Brain Res, 2006) and in animals (Ray et al., J Neurosci, 2008), and have been used to map normal brain function and to decode commands in brain-computer interfaces. To understand the role that high-gamma activity (HGA) plays in both normal and pathological brain states, deeper insights into its generating mechanisms are essential. Because the neural populations recorded by LFPs and EEG cannot be comprehensively recorded at scales that are likely to be relevant, we used a biologically based computational model of a cortical network to investigate the mechanisms generating HGA.

Methods: The computational model included excitatory pyramidal regular-spiking (PY) and inhibitory fast-spiking (I) neurons described by Hodgkin - Huxley dynamics. We compared activity generated by this model with HGA that was observed in LFP recorded in monkey somatosensory cortex during vibrotactile stimulation. These animal data were used because simultaneously recorded LFP and single unit activity were available, in contrast to the human case. Sensory input was modeled as uncorrelated Poisson spike input arriving to subpopulation of excitatory and inhibitory neurons. Input rate was modeled as fast ON response followed by slowly decaying response simulating responses of fast adapting and slowly adapting receptors to step stimulation.

Results: Increase of firing rate and broadband HGA responses in LFP signals generated by the model were in agreement with experimental results (Figure). Blocking the I'!PY connections in the model abolishes the HGA while blocking PY'!I, PY-PY or I-I does not. Thus, these HGA appear to be mediated mostly by an excited population of inhibitory fast-spiking interneurons firing at high-gamma frequencies and pacing excitatory regular-spiking pyramidal cells, which fire at lower rates but in phase with the population rhythm. HGA were generated for a broad range of model parameters and sensory input values and did not require setting the network close to pathological regime.

Conclusions: HGA reflects local cortical activation under normal conditions and as such is a good candidate for mapping cortical areas engaged by a specific task. Pathological conditions are not necessary to observe HGA in the model. There might be different mechanisms leading to activity in similarly high frequencies and frequency alone may not be sufficient to distinguish between normal and pathologic oscillatory activity. The mechanisms of HGA, in this model of local cortical circuits, appear to be similar to those proposed for hippocampal ripples generated by subset of interneurons that regulate discharge of principal cells.

IMAGE: images/908031_A.jpg

1.055

RAPAMYCIN SUPPRESSES MOSSY FIBER AND SOMATOSTATIN INTERNEURON AXON SPROUTING BUT NOT EPILEPTOGENESIS IN A MOUSE MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: Patients with temporal lobe epilepsy display many pathological changes in the dentate gyrus, including hilar neuron loss, granule cell axon (mossy fiber) sprouting, GABAergic axon sprouting, ectopic hilar granule cells, and others. It is unclear which of these circuit anomalies, if any, contribute to epileptogenesis. To address that issue, one would like to selectively block specific changes and identify those that affect development of spontaneous seizures. Recent evidence suggests the mTOR inhibitor, rapamycin, might be useful in this regard.

Methods: GIN mice, which express GFP in a subset of somatostatin interneurons, were treated with pilocarpine to induce status epilepticus. Beginning 1 d later, mice were treated daily with rapamycin (3 mg/kg, ip). To evaluate epileptogenesis, mice were video-monitored daily 9 h/d during the second month after pilocarpine-induced status epilepticus. To more rigorously evaluate epileptogenesis, mice were video-EEG monitored with an electrode implanted in the hippocampus. Recordings were obtained daily 9 h/d during the third month after status epilepticus.

Results: After 2 months, rapamycin-treated mice displayed less mossy fiber and less GFP-positive axon sprouting in the granule cell layer + molecular layer compared to vehicle-treated controls. Hilar neuron loss, number of granule cells, and number of Prox1-immunoreactive hilar ectopic granule cells was similar in rapamycin- and vehicle-treated epileptic mice. The frequency and severity of seizures was similar in rapamycin- and vehicle-treated mice.

Conclusions: One interpretation of these data is that axon sprouting in the dentate gyrus is not epileptogenic but hilar neuron loss and generation of ectopic granule cells might be. However, mossy fiber and somatostatin axon sprouting might have opposing effects, and rapamycin might affect epileptogenesis through other mechanisms that were not evaluated in the present study. Nevertheless, these findings suggest that targeting signal transduction mechanisms is a useful strategy to more selectively test the epileptogenicity of circuit changes in temporal lobe epilepsy.

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1.056

SLOW CHANGES IN FUNCTIONAL CONNECTIVITY DURING EPILEPTOGENESIS IN A SPONTANEOUSLY SEIZING ANIMAL MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: Temporal lobe epilepsy, the most common of the epilepsies, is characterized in the brain by sclerosis, fiber sprouting, and the eventual emergence seizures. Epileptogenesis is defined as the progressive slow process between when the normal healthy brain transitions into a diseased state over months to years. Ictogenesis describes how the epileptic brain transitions from normal state to seizure on a shorter time scale of seconds to minutes. Previous results show Granger causal interactions from the dentate gyrus (DG) to the CA1 increase during ictogenesis, while the interactions from the CA1 to the DG remain constant. Our hypothesis is that slow changes in the functional connectivity of the temporal lobe occur during epileptogensis are indicative of potential network level reorganization underlying the eventual emergence of seizure behavior. Additionally, previous work using magnetic resonance imaging show specific gradual structural changes in the temporal lobe during epileptogenesis that support this hypothesis.

Methods: We use a spontaneously seizing animal model of temporal lobe epilepsy that is continuously monitored electrophysiologicaly using 32 channel microarray electrodes over 6-8 weeks. This model produces electrophysiological data that enables us to study

epileptogenic and ictogenic transitions using functional and effective connectivity measures such as correlation and Granger causality.

Results: An analysis of functional connectivity using normalized covariance over the longer time scale of epileptogenesis demonstrates the slow degradation of functional connectivity within the hippocampus post stimulation into status epilepticus relative to age matched controls. A circadian like cycle embedded within the cross correlation measure. Qualitative analysis suggest that this pattern is disrupted post status epilepticus, a result consistent with previous studies in our lab using this animal model.

Conclusions: The abnormal functional connectivity patterns seen during seizure epochs suggest that specific functional changes have occurred within the hippocampal-entorhinal network . Indeed, long term changes in functional connectivity seen during epileptogenesis support the hypothesis that functional connections within the limbic networks are changing gradually over time rather than large acute changes following status epilepticus.

1.057

GENE PROFILING OF THE CA1 AFTER MULTIPLE EARLY-LIFE SEIZURES

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Rationale: Although early-life seizures may be harmful and increase the risk of epilepsy later in life, postnatal seizures acquired due to asphyxia or other early traumas may lead to tolerance to prepare the brain from the impact of a subsequent injury. Previously, we demonstrated that postnatal (P) P20 juvenile rats are sensitive to CA1 injury following a single injection of kainic acid (KA) (1xKA) but resistant to this damage when the animals have a history of two prior seizures on P6 and P9 (3xKA). We hypothesized that the two earlier seizures, in the neonatal period, led to neuroprotection via a pre-conditioning mechanism involving attenuation of Ca2+ currents and induction of survival signaling pathways.

Methods: The CA1 was microdissected away from the other hippocampal subregions and total RNA was extracted, subjected to RT-PCR then hybridized with a rat microarray platform to identify genes involved in the protective effects produced by multiple early-life seizures. Ca2+ influx with FURA 2-AM imaging was used to monitor glutamatergic receptor efficacy after 1xKA vs. 3xKA.

Results: Microarray results indicated that over 13,000 genes were regulated in the CA1 after a single seizure induced in the juvenile period, but also that a large percentage of them were differentially regulated if the animals had a history of two neonatal seizures. Of the total number of altered genes only 11 were commonly decreased and 389 were commonly increased. Examples of protective genes that were up-regulated after 3xKA were anti-apoptotic Bcl-2 gene members and adaptor proteins such as adaptor protein complex AP-1, sigma 1 adaptor protein, phosphotyrosine interaction, and adaptor-related protein complex 3, mu 2 subunit. Differential regulation of cytokines also favored protection. Annexins and S100 proteins two large, but distinct, calcium-binding protein families were differentially regulated; annexin 3 was increased after 3xKA but not after 1xKA. Calmodulin 2 was decreased after 1xKA but increased after 3xKA. Ca2+ imaging studies also showed that N-methyl-D-aspartate (NMDA) responses were enhanced at 5 hrs after 1xKA but these elevations were attenuated after 3xKA.

Conclusions: Described changes may contribute to early-life seizure-induced pre-conditioning and neruroprotection. This could be achieved by reduced glutamate receptor-mediated Ca2+ permeability of the hippocampus and redirecting apoptotic pathways.

1.058

A NOVEL METHOD FOR THE SEPARATION AND MEASUREMENT OF ALLOPREGNANOLONE AND OTHER PREGNANOLONE NEUROSTEROIDS IN CEREBROSPINAL FLUID AND SERUM

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Rationale: Neurosteroids are important modulators of neuronal activity. Allopregnanolone, a metabolite of progesterone, and other endogenous neurosteroids are of particular interest in epilepsy. Allopregnanolone has a stereospecific affinity for the GABA-A receptor and has been found to be a potent anticonvulsant in animal models. The measurement of neurosteroids in biological samples requires a sensitive and specific assay. Although prior studies have demonstrated the feasibility of measuring endogenous neurosteroids in CSF and serum, background interferences from biological matrices limit sensitivity. Also, allopregnanolone is one of four possible pregnanolone stereoisomers produced from progesterone by stereospecific isoenzymes and the complete separation of these pregnanolone isomers has not been achieved. Our method for the separation and measurement of allopregnanolone and other pregnanolones has the advantage of extremely high chromatographic resolving power, sufficient to separate pregnanolone isomers, as well as very high sensitivity.

Methods: Samples were heated with triethylamine sulfate to denature any protein in the biological matrix. Steroids were extracted using a C18 column followed by a Sephadex LH-20 column to further purify the pregnanolone fraction containing allopregnanolone and its three stereoisomers isopregnanolone, epipregnanolone, and pregnanolone as well as pregnenolone, a precursor of progesterone. After further purification by HPLC, samples were derivatized in two steps, first with methoxyamine hydrochloride, then tert-butyldimethylsilyl imidazole. The derivatized samples were passed through a Lipidex 5000 column, dried and reconstituted in hexane for GC-MS analysis.

Results: Using our method, we were able to achieve excellent chromatographic separation and quantification of individual pregnanolone isomers and pregnenolone. By monitoring the ion m/z 404 for the pregnanolone isomers, and m/z 402 for pregnenolone, these species were characterized in a single run (Figure 1). The use of the methyloxime t-BDMS derivative (MO-tBDMS) afforded greater specificity, and improved sensitivity over other derivatives we tested, because it increases the molecular weight of the steroids and directs the fragmentation to the t-BDMS group. Our limit of detection, for a mixture of pregnanolones and pregnenolone standards in a serum matrix, was 300 femtograms on column. The recovery of each steroid was excellent and gave good linearity over a very low concentration range (Figure 2). Sample concentrations ranged 0.6 to 40 picograms on column.

Conclusions: We have developed a new assay for the measurement of low concentrations of pregnanolones and pregnenolone that features a solid-phase extraction step, followed by isolation and purification of these steroids using a combination of a lipophilic gel chromatography

and HPLC. This has been a distinct and novel feature of our assay development that renders the samples of sufficient purity to permit detection and quantification of these neurosteroids in small quantities of serum and CSF.

IMAGE: images/907695_A.jpg

IMAGE: images/907695_B.jpg

1.059

TLE PATIENTS SHOW THE HEMISPHERIC LATERALIZATION OF THE AUTONOMIC FUNCTIONS

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Rationale: Hemispheric lateralization of the autonomic functions is not well known. We studied this in temporal lobe epilepsy (TLE) patients with the following questions- (1) Does interictal epileptogenic activity in temporal lobes have a differential affect on autonomic functions? (3) Does abolishing interictal epileptogenic activity in TLE after surgery result in comparable autonomic functions between the right TLE (RTLE) and left TLE (LTLE)patients.

Methods: The study was conducted on 30 RTLE patients, age (22.03±12.31)yrs and 23 LTLE patients, age (25.13±10.27)yrs. Autonomic functions were assessed using standard battery of reactivity test and short term HRV before and at 3 & 6 months after surgery.

Results: Fall in SBP during HUT (p=0.025) and HR (p=0.001) and E:I (p=0.001) ratios during DBT were significantly higher in the LTLE group. Similarly in the measures of HRV; SDSD (p=0.021) and RMSSD (p=0.045) were also significantly higher in the LTLE patients. After surgery all the above mentioned variables become comparable at 3 & 6 months while, DBP (p=0.005) in CPT became higher in LTLE patients.

Conclusions: We found that in the presence of epileptogenic stimulation LTL is dominant for the parasympathetic activity and reactivity while; RTL is dominant for the sympathetic reactivity. After surgery the autonomic functions became comparable except sympathetic reactivity which became higher in LTLE. Our study suggests that there is a relative but definite laterality exists in the autonomic functions in TLE patients.

1.060

PERMANENTLY IMPAIRED MITOCHONDRIAL REDOX STATUS AND OXIDATIVE/NITROSATIVE STRESS DURING EPILEPTOGENESIS

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Rationale: Reactive oxygen and nitrogen species (ROS/RNS) are mediators of oxidative stress but also function as second messengers in redox signaling. Mitochondrial dysfunction and oxidative stress are consequences of seizure activity but their contributing role to epileptogenesis is largely unknown. The goal of this study was to determine the extent of mitochondrial and tissue redox status and indices of oxidative and nitrosative stress during chemoconvulsant-induced epileptogenesis.

Methods: Adult Sprague-Dawley rats were injected with vehicle, kainate or lithium and pilocarpine and chronically monitored with video and EEG for seizure activity for up to 12 weeks. Evidence of altered redox status and reactive species production and damage was measured at different time points during epileptogenesis i.e. shortly after induction of status epilepticus, prior to development of epilepsy (i.e. seizure-free latent period), and during the chronic stages of epilepsy.

Results: In the lithium-pilocarpine model a time-dependent increase in hydrogen peroxide (H_2O_2) production that coincided with increased mitochondrial DNA (mtDNA) lesion frequency in the hippocampus was observed during epileptogenesis. In the kainate model a 20-25% increase in nitrite levels was observed shortly after treatment (8h-48h) and the 3-nitrotyrosine/tyrosine ratio increased 2-10-fold throughout all stages of epileptogenesis in the kainate and lithium-pilocarpine models. The mitochondrial redox status measured by reduced coenzyme A and its disulfide with glutathione (CoASH/CoASSG) was decreased 70-80% shortly after kainate and lithium-pilocarpine treatment and remained permanently decreased at all chronic time points. Hippocampal tissue redox status measured by glutathione (GSH) and its disulfide, GSSG, was decreased approximately 60% and remained permanently decreased throughout epileptogenesis in both the kainate and lithium-pilocarpine models.

Conclusions: The production of ROS/RNS during the “latent period” and acute and chronic phases of epileptogenesis and a permanent alteration of mitochondrial and tissue redox status in two independent animal models of temporal lobe epilepsy suggest that redox-dependent processes may contribute to the progression of epileptogenesis.

1.061

A EUROPEAN DATABASE OF CLINICAL AND EEG DATA FROM PATIENTS WITH EPILEPSY

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Rationale: A growing number of research groups worldwide works on the application of advanced analysis methods for EEG data. Long-term EEG data are of particular interest e.g. for the development and evaluation of spike and seizure detection algorithms as well as for time series analyses for seizure prediction. Available EEG data are scarce. We here report progress in the development of a European EEG database containing abundant metadata as part of the European Project EPILEPSIAE (www.epilepsiae.eu). This work has been approved by the ethics committies of the participating centers and is supported by the European Union (grant 211713).

Methods: A relational database scheme was developed for annotated long-term EEG data, derived features, MRI data, and clinical metadata including seizure time points, patterns and spread of ictal activity, and typical spike topographies. Data from three European epilepsy centers (Coimbra, Freiburg and Paris) are being integrated into the database. A web client was programmed for queries on predefined datasets and for accessing data.

Results: As of June 2010, more than 150 patients with long-term continuos EEG datasets of at least 4 days duration have been included in the database. These data include more than 1000 clinical ictal events as well as interictal periods of interictal EEG. Patients both with surface and intracranial EEG have been integrated. Presently, EEG data at

higher sampling frequencies of 1000-2500 kHz are additionally introduced.

Conclusions: There is considerable progress in this database which sets a new standard for EEG time series analyses and allows for new applications, e.g. subgroup analyses of algorithms for particular EEG syndromes, and intraindividual training and testing of algorithmic performance. It is considered to open access to this European database to research groups from 2012 on.

1.062

CORRELATION BETWEEN INTERICTAL HIGH-FREQUENCY OSCILLATIONS AND SEIZURE OUTCOME IN PEDIATRIC RESECTIVE EPILEPSY SURGERY

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Rationale: High-frequency oscillations (HFOs) >80 Hz (ripples at 80-200 Hz and fast ripples [FRs] at >250 Hz) have been recorded in the intracranial electroencephalogram (EEG) from the epileptogenic brain. There has been no diagnostic modality to date to measure the epileptogenic zone directly. Interictal HFOs may be a valuable marker to localize the epileptogenic zone, removal of which is necessary and sufficient to achieve seizure freedom. We evaluated correlation between resection of the brain region with interictal HFOs and seizure outcome using automated detection of HFOs.

Methods: We retrospectively analyzed 27 pediatric patients (2-18 years) with intractable epilepsy who underwent intracranial video EEG before tailored surgical resection between July 2005 and June 2008. Intracranial EEGs were sampled at 1 kHz using 52-124 channels. For each patient, we analyzed 10 epochs of 2-minute EEG during non-rapid-eye-movement sleep, which were separated from each other and seizure sections by e”1 hour. We calculated the rate (/min) of ripples and FRs for each channel in bipolar montage after automated detection by a custom-made software written in MATLAB (The MathWorks, USA). Subsequently we determined the channels with high-rate HFOs (ripples, FRs). We calculated HFO measures including *resection ratio* (= area of surgical resection / area covered by electrodes), *HFO area ratio* (= area with high-rate HFOs / area covered by electrodes) and *HFO resection ratio* (= area with high-rate HFOs within surgical resection / area with high-rate HFOs). We determined seizure outcome at 1 year after surgery according to the proposed outcome classification (classes 1-6, class 1 being the best) by ILAE in 2001. We compared these HFO measures between good (classes 1-2) and poor (classes 3-6) outcome groups by Wilcoxon’s rank sum test. We also tested the effect of these HFO measures on seizure outcome by multivariate ordinal logistic regression analysis. We analyzed patients with HFOs in e”3 channels separately from those with HFOs in <3 channels.

Results: Thirteen had good (classes 1-2) and 14 patients had poor seizure outcome (classes 3-6). Twenty-two patients (good outcome 11, poor 11) had high-rate ripples in e”3 channels. Nineteen (good 10, poor 9) had high-rate FRs in e”3 channels. *HFO resection ratio (FRs)* was higher in the good outcome group than the poor (median 100% vs. 75%, p = 0.04). Conversely, higher *HFO resection ratio (FRs)* predicted better seizure outcome (p = 0.02, odds ratio = 1.09 [1.01-1.17]). *HFO area ratio (ripples)* and *HFO resection ratio (ripples)* had no correlation with seizure outcome. The HFO measures for patients with HFOs in <3 channels did not have effect on seizure outcome.

Conclusions: Interictal FRs are indicative of the epileptogenic zone if they are present in at least 3 channels. Interictal ripples are considered to reflect the irritative zone rather than the epileptogenic zone.

1.063

PERI-ICTAL HEART RATE VARIABILITY IN SUBJECTS WITH PARTIAL EPILEPSY

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Rationale: Heart rate variability (HRV) is a useful tool in the evaluation of the autonomic nervous system and decreased HRV measures have been found to be negative prognostic markers of cardiovascular mortality. Autonomic effects on heart rate have been well documented during seizures, and some of these changes have been implicated as plausible mechanisms of SUDEP. This study compares peri-ictal HRV in patients with partial epilepsy and psychogenic non-epileptic seizures.

Methods: This is a retrospective study of patients evaluated at our epilepsy monitoring unit during 2009. Subjects with a diagnosis of partial epilepsy or psychogenic nonepileptic seizures (PNES) were included. Subjects with PNES were used as the control group. Time-domain measures of HRV were calculated during the pre-ictal and ictal periods using ten-second electrocardiogram recordings. The values for the standard deviation of all RR intervals (SDNN) and the root-mean-square successive difference (r-MSSD) were obtained using the Kubios 2.0 software. Differences between age, gender, pre-ictal HRV and ictal HRV were assessed using a Wilcoxon rank-sum test. P-values < 0.05 were regarded as statistically significant.

Results: Twenty-two patients were included, 12 patients had PNES and 10 subjects had partial epilepsy (5 with temporal lobe epilepsy: TLE). No significant differences (pe” 0.05) in age or gender were found between the two study groups. During the pre-ictal or ictal period, no significant differences in HRV were found between the subjects with partial epilepsy and PNES. However, during the ictal period, subjects with TLE had significantly lower measures of SDNN (p<0.045) and r-MSSD (p<0.018) when compared to subjects with PNES.

Conclusions: In this study, we found decreased HRV measures in seizures originating from the temporal lobe compared to psychogenic events confirmed by video EEG. Our results suggest that decreased ictal HRV in patients with TLE is not solely due to psychological apprehension towards an upcoming seizure. Significant changes in HRV may be seen more frequently in TLE than other types of partial epilepsy due to the proximity of the temporal lobe to the insular cortex, which may exert influences on cardiovascular autonomic control. At present, it is unknown whether decreased HRV measures are a risk factor for SUDEP in patients with intractable epilepsy. This deserves further investigation and prospective studies, since the development of useful clinical markers for the detection of patients at risk of SUDEP may help guide therapeutic interventions in the future. We are actively recruiting patients for this study.

1.064

DETECTION AND CLINICAL OUTCOME OF STATUS EPILEPTICUS IN PATIENTS UNDERGOING CONTINUOUS EEG MONITORING

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Rationale: Continuous EEG (cEEG) monitoring involves prolonged recording of EEG and is typically performed at the bedside in critically ill, hospitalized patients. It is increasingly being used to evaluate patients for unexplained change in mental status, detection of subclinical (nonconvulsive) seizures and management of status epilepticus (SE). The diagnostic yield of the test has not been fully characterized. There are no definite recommendations regarding how long it should be continued before nonconvulsive seizures or status epilepticus are excluded, and when to stop the study after controlling seizures. Its influence on the clinical outcome of SE has not been established.

Methods: All adult patients who underwent cEEG monitoring between 01/01/2007 and 03/15/2010 at Penn State University Hershey Medical Center were included in this retrospective study. Video was simultaneously recorded with cEEG at the bedside in all patients. Patients admitted electively to the epilepsy monitoring unit for diagnostic or presurgical evaluation were excluded.

Results: 132 patients were identified. Of these, 60 were males and 74 were females. The mean age of the patients at the time of the cEEG was 59.5 years (range: 22-94 years). The mean duration of cEEG monitoring was 58.2 hours (range: 4-360 hours). 55 (41.6%) patients had status epilepticus. Of these, 19 (35%) had clinical status epilepticus (CSE) and 36 (65%) had only nonconvulsive status epilepticus (NCSE). Among all patients with status epilepticus (CSE and NCSE), 15 (27%) patients had recurrence of nonconvulsive seizures after initial resolution of the status. In 3 (5%) patients, SE was not noted during the initial portion of the cEEG recording but was identified within 24 hours, and in 2 (3%), SE was detected only after 24 hours of cEEG monitoring. In addition, in 2 (3%) patients, SE was not identified in an initial routine 30-minute EEG performed before cEEG was started. 36 (27%) of all patients who underwent cEEG died. Among patients with SE, 22 (40%) died, 7 (13%) were discharged to a long term acute care hospital, 10 (18%) were discharged to an acute rehabilitation facility, 3 (5%) were discharged to other facilities, and 13 (24%) recovered fully and were discharged home.

Conclusions: cEEG monitoring is helpful in the accurate diagnosis and optimal management of SE. It enables the identification of NCSE in a substantial proportion of patients as the sole manifestation of SE or following resolution of CSE. Most seizures are detected within the first 24 hours but longer monitoring may be required in some patients. Routine EEGs or initial portions of cEEG monitoring may fail to record NCSE. Status epilepticus is associated with high mortality and morbidity, but early detection and treatment of nonconvulsive seizures and status using cEEG may improve the clinical outcome.

1.065

IS HIGH FREQUENCY ICTAL EEG ASSOCIATED WITH FAVORABLE SURGICAL OUTCOME?

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Rationale: Intracranial EEG (iEEG) is performed in pharmacoresistant partial epilepsy patients when non-invasive tests are incongruent or putative ictal onset zone is near eloquent cortex. Determining ictal onset zone using iEEG has been conventionally based on the identification of specific ictal patterns in the bandwidth of 1- 70 Hz. High frequency oscillations (HFOs, > 60 Hz) have been recently recognized as highly correlated with epileptogenic zones. However, HFOs can be difficult to detect in the time domain because of small amplitude and low sampling rate (256-512 Hz) of current clinical EEG system. Therefore, true incidence of ictal HFOs and its role in localization of epileptogenic zone on iEEG remain elusive.

Methods: From September 2008 to Dec 2009, we identified 47 patients (mean age = 10 yrs, range 9 mo to 25 yrs; M:F = 28:19) who had iEEG, high frequency domain analysis, and subsequent resective surgery. iEEGs were recorded with 2000 Hz sampling rate and examined visually in the 1-70 Hz bandwidth. iEEG during a patient's habitual seizure was further analyzed with time-frequency decomposition in three additional frequency bandwidths: 80-150, 150-300, 300-500Hz. Each individual electrode was also carefully evaluated for the leading edge of HFO (primary ictal onset zone, PIZ) in the fast Fourier Transformation power spectrum and compared with the visually apparent onset in the time domain. In addition to the seizure onset, the spread of HFOs during a seizure (secondary ictal spread zone, SIZ) before generalization was also analyzed in the same bandwidths. The completeness of resection was determined based on the inclusion of PIZ and SIZ in the resection margin. Surgical outcome was scored using Engel's classification at 6 mo, 1 yr, and 2 yr post-operatively.

Results: Overall seizure-free outcome in 47 patients was 46% (22/47) (mean follow-up duration 10 mo, 6 - 18 mo). Forty-four (94%) of 47 patients had ictal HFO by time-frequency decomposition analysis on iEEG. Ictal HFO frequency was distributed in all three bandwidths: 11, 80 - 150; 16, 150-300; 7, 300 - 500 Hz bandwidth. Unlike the HFOs with two lower bandwidths, the highest frequency (300 - 500 Hz) ictal HFOs tended to remain in the same electrodes during a seizure until it generalized. Thirty four patients (77%, 34/44) had complete resection including PIZ and SIZ while the other 10 patients (23%, 10/44) had incomplete resection because of involvement of eloquent cortex. Complete resection of ictal HFOs resulted in significantly higher seizure freedom (56%, 19/34) than incomplete resection (10%, 1/10) (Fisher's Exact Test, $p = 0.013$). Among the patients who had complete resection of ictal HFOs, different bandwidths did not affect surgical outcome.

Conclusions: Our study showed that ictal HFO is commonly found in iEEG and has a localizing value. The presence of ictal HFOs and its complete resection may be one of the favorable prognostic indicators for surgical outcome.

1.066

INTO THE SPECTRUM OF HYPERKINETIC SEIZURES: A CLINICAL-KINEMATIC AND SEEG STUDY

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Rationale: The aim of this study was to characterize different motor patterns of hyperkinetic (HK) seizures and to investigate their possible different subtending anatomo-functional correlates.

Methods: 60 patients presenting drug resistant epilepsy with HK seizures have been studied by video-EEG and stereo-EEG (SEEG) (52 cases), preliminary to epilepsy surgery; 699 seizures have been recorded. Video-EEG data allowing the analysis of HK manifestations underwent clinical and kinematic study, consisting in the estimation of displacement, speed and acceleration of body segments with a computerised system (Videopoint), to clarify the relationship between cyclic motor activity of trunk and proximal and distal parts of the four limbs. A study of correlation of the hyperkinetic manifestations with the topography of the SEEG discharge has been performed.

Results: Based on the topography and the characteristics of the motor manifestations we have classified the HK seizures in 5 subgroups:

1) a "symmetrical" pattern (10 patients, 66 seizures), with bilateral HK movement of trunk and limbs;

2) an axial pattern (17 patients, 161 seizures), usually preceded by body pronation and mainly characterized by rhythmic oscillations of the trunk and minor involvement of the limbs;

3) an hemi-lateral pattern (14 patients, 131 seizures), with rhythmic, wild motor activity predominant in the limbs of one side and concomitant dystonic or hypertonic posturing of the contralateral one;

4) an hemi-vertical pattern (9 patients, 158 seizures), with HK manifestations prominently involving lower limbs, with hands usually immobilized behind the head or grasping;

5) a "puppet" pattern (10 patients, 183 seizures) with fragmentary, arrhythmic HK manifestations.

Eight cases showed a slow motor activity, 5 of them post-surgical ablation. Kinematic analysis confirmed strong analogies in subgroups 1-4, with different somatic topography, and substantial qualitative differences in subgroup 5.

SEEG analysis of the ictal discharged showed that the ictal onset zone could be extremely variable, but the symptomatogenic zone of HK manifestations was always located in the fronto-mesial region, with a strong involvement of the cingulate gyrus. Whereas subgroups 1-3 showed only minor differences in the ictal SEEG correlates, group 4 presented a concomitant fronto-temporal discharge, homolateral to HK manifestations, and group 5 had also prominent fronto-lateral discharge.

Conclusions: Steaming from the concept that HK seizures represent an heterogeneous entity, we propose a clinical classification of HK patterns, possibly suggesting the ictal involvement of different motor circuits.

1.067

PREVALENCE OF NON-CONVULSIVE SEIZURES DUE TO CEREBRAL HEMORRHAGE IN THE ICU

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Rationale: Hemorrhage involving structures in or around the brain, including intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and subdural hematoma (SDH), is associated with significant morbidity and mortality. One mechanism by which cerebral hemorrhage (CH) can cause further brain injury is through the generation of epileptic seizures. Epileptic seizures are a potentially treatable brain disorder; however, sub-clinical seizures are difficult to detect.

Methods: We reviewed the records of over 950 patients consecutively admitted to the Intensive Care Unit from January 1, 2007 until May 31, 2010 with a diagnosis of SDH, SAH, or ICH. All EEG studies were performed on patients in the ICU. Epileptiform EEG abnormalities were characterized as spikes, sharp waves, PLEDs, or electrographic seizure activity. Non-epileptiform abnormalities were also characterized.

Results: Routine EEG (rEEG) or continuous EEG (cEEG) was performed on 20% of all patients, with approximately equal percentages regardless of type of CH. Slowing was the most common electrographic finding. In this study population, the prevalence of epileptiform findings was 35% and of ictal findings was 25%, with no significant difference found between SAH, SDH, ICH. Continuous EEG detected ictal activity in a much higher percentage of cases than rEEG. In nearly all cases with ictal features, seizure activity was sub-clinical, and compatible with the diagnosis of non-convulsive status epilepticus.

Conclusions: Cerebral hemorrhage is a significant cause of sub-clinical seizure activity. The fact that over 700 patients with CH did not ungergo EEG evaluation suggests that the diagnosis of sub-clinical seizures was missed in over 200 cases. Missing the diagnosis of sub-clinical seizures would be expected to have a negative impact on patient outcome, especially in this patient population. Continuous EEG is an important diagnostic tool in patients in the ICU setting and a more detailed analysis of the relationship of seizures in the acute setting of CH and outcome is warranted.

1.068

CYCLIC ELECTROGRAPHIC SEIZURES IN CHILDREN: A UNIQUE EEG PATTERN OF STATUS EPILEPTICUS

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Rationale: The cyclic seizure (CS) pattern was initially reported in patients with critical illness. This CS EEG pattern is difficult to appreciate on standard EEG recordings and CS are best detected using digital trending analysis (DTA) applied to standard EEG. In this study, we examined the incidence, clinical and EEG features of CS in children with Status Epilepticus (SE).

Methods: The EEG reports of all children (0-18 years) diagnosed with SE were reviewed (2002-2010). Children with repetitive seizures (>2 seizures on the same EEG recording) were identified based on the EEG report, the EEG files were retrieved for review, and DTA applied to further assess the EEG features of CS. Subsequently, clinical and EEG features of children with SE and CS were reviewed and compared to children without CS.

Results: A total of 279 children were identified with the diagnosis of SE in which febrile SE (FSE) occurred in 106 (38%), non-convulsive SE (NCSE) in 12 (4.3%) and newborn SE in 6 (2.2%) patients. Refractory status epilepticus (RSE) occurred in 21 (7.5%). EEG recording was obtained in 173 (62%). The diagnosis of epilepsy was present in 78 (28%).

Repetitive EEG seizures were identified in 34 children; 28 (82%) of these had CS subsequently identified. The mean age was older in CS group (5.4±5.1) compared to non-CS group (3.8±3.8) (p: 0.047). In CS group, twelve (43%) were previously healthy, 16 (57%) had developmental delay,16 (57%) had epilepsy and 9 (32%) had with RSE. Only two children with FSE had CS. The entire duration of the CS pattern ranged from 20 min to 10 hr, individual seizure duration from 30 seconds (sec) to 180 sec, and inter-seizure interval from 40 sec to 300 sec. Except for one, focal seizures occurred in all with CS. Non-convulsive seizures (NCS) were identified in 13 (46%), and NCSE in 5 (18%). Developmental delay (57% vs 36%, p: 0.034), a history of epilepsy (57 vs 28%, p: 0.07), and RSE (33% vs 7.5%, $p<0.001$) were seen more often in CS group. CS was rarely reported in association with FSE (p: 0.001). SE presenting with focal clinical features, repetitive clinical seizures, RSE, and history of epilepsy are the strong predictors for cyclic seizures ($p<0.05$). Age, gender, and developmental delay were not risk factors for CS.

Conclusions: CS are not uncommon in children with SE. CS are difficult to recognize using standard EEG recordings and best detecting using DTA. Overall, CS occurs in one out of ten children with SE and in slightly over one half of children with an acute exacerbation of epilepsy. In addition, this CS pattern may predict RSE. Therefore, this unique EEG pattern requires special attention during the treatment of SE and may give insight into the pathophysiology of SE.

1.069

SAFETY OF PROLONGED VIDEO-EEG MONITORING IN A TERTIARY PEDIATRIC EPILEPSY MONITORING UNIT

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Rationale: Prolonged video-EEG (VEEG) monitoring is an invaluable tool in the diagnosis and treatment of epilepsy and unclassified events. Previous reports from the adult literature have demonstrated an increased risk of status epilepticus and injury from seizures during the examination. The goal of our study was to review the safety and utility of our pediatric epilepsy monitoring unit (PEMU) experience.

Methods: We retrospectively reviewed the PEMU reports and charts of 225 patients 18 years of age and younger with 241 admissions totaling 768 days at our tertiary hospital from January 1, 2009 to December 31, 2009. Demographic information, final event diagnoses, quantity of events, duration of events and medical complications due to monitoring were analyzed.

Results: Of the 241 admissions to the PEMU, 106 (44.0%) captured epileptic seizures, 79 (33%) demonstrated non-epileptic events (NEE), and 36 (15%) failed to capture any events. The average length of stay was 3.2 days. The patients had a mean age of 9.4 years old with 113 males (47%). 20 (8.3%) evaluations were for the presence or absence of continuous spike and wave of slow-wave sleep of which 11 were positive. Five patients underwent intracranial monitoring (4 subdural grids and 1 depth wire). Medical complications include: 1 fall due to seizure, 1 subdural fluid collection associated with grid placement causing paresis, and 1 patient with hip pain following a seizure. No patients had any long-term complications. In evaluating the rate of status epilepticus, defined as seizure lasting longer than 15 minutes, 6 patients had 8 episodes. This constitutes 2.5% of all admissions and 5.1% of admissions with epileptic seizures. The median duration was 26 minutes and the mean duration was 67 minutes with 2 patients requiring transfer to the pediatric intensive care unit. Rescue medications were used in 11 patients (5.8%) of admissions, including 3 patients who had non-epileptic events.

Conclusions: Medical complications from seizures occurring during VEEG monitoring are an increasing area of concern regarding patient safety. In comparison to some published adult literature, our patients experienced a higher rate of status epilepticus but a lower rate of medical complications. We also had a relatively short length of stay with a surprisingly high number of NEE. The 3 patients with NEE who received rescue medications highlights a need for improved real-time interpretation of VEEG data as it is being recorded to avoid over treatment. Overall, our study suggests that prolonged VEEG monitoring in the pediatric age group appears to be a safe diagnostic procedure.

1.070

VALIDATION OF AN AUTOMATED NEONATAL SEIZURE DETECTOR: A CLINICIAN'S PERSPECTIVE

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Rationale: Majority of neonatal seizures occurring in the neonatal ICU (NICU) are subclinical, being detected only by EEG monitoring. Expertise for recording and interpretation of EEG is not available around the clock in a NICU, resulting in a need for a reliable, automated EEG-based seizure detection method.

Aim: To validate an improved automated neonatal seizure detection algorithm, in a large and independent data set of neonatal seizures recorded during continuous EEG monitoring and to evaluate its performance in relation to EEG background.

Methods: We classified EEG background into eight grades based on evolution of discontinuity over 24 hours and presence of sleep-wake cycles. Patients were further sub-classified into two; gpI: those with mild to moderate (grades 1-5) and gpII: severe (grades 6-8) abnormalities of EEG background. Seizures were categorized as definite and dubious. Seizure characteristics were compared between the two EEG groups. The neonatal seizure detection algorithm (Deburchgraeve W. et al., Clin Neurophysiol 2008;119:2447-54)was developed jointly by the department of Electrical Engineering at the Katholieke Universiteit, Leuven and the department of Clinical Neurophysiology at the Erasmus MC, university medical center in Rotterdam. It has been further improved in artifact rejection. The algorithm was tested offline on a large new ('unseen') EEG data set of 756 hours of monitoring from 24 consecutive neonates (median 25h per patient) with encephalopathy and recorded seizures. No selection was made regarding quality of EEG or presence of artifacts.

Results: Seizure amplitude showed a significant negative correlation with worsening EEG background grade (Spearman's rho= -.475, p=0.019). In patients in EEG gpII, the total number of seizures expressed was significantly increased while the amplitude of the seizures was significantly decreased (Table 1 & Fig 1). There was a tendency for patients in this group to express more seizures with higher firing frequency, increased percentage of arrhythmic seizures and shorter duration of seizures (Fig 1), though the results were not statistically significant. After excluding 4 patients with persistent, severely abnormal EEG background, and predominantly (>90%) dubious seizures characterized by low amplitude arrhythmic discharges, the algorithm showed a median sensitivity per patient of 86.9% (1263/

1538 seizures detected, total sensitivity 82.1%), positive predictive value (PPV) of 89.5% and false positive rate of 0.28/h. Sensitivity tended to be better for patients in gpI.

Conclusions: The algorithm detects neonatal seizures well, has a good PPV, and is suited for long-term EEG monitoring. The changes in electrographic characteristics like amplitude, duration and rhythmicity in relation to worsening EEG background tend to negatively affect the performance of automated seizure detection.

Table 1. Comparison of neonates with mild to moderate (gp I, grades 1-5,) and severe (gp II, grades 6-8) EEG background abnormality

IMAGE: tables/906524_T1.jpg

h:hours, Sz: seizure, Arrhyth sz %: percentage of seizures that were arrhythmic. * : for the final analysis, 4 patients in gp II with persistent severe abnormality of EEG background and having predominantly dubious seizures were excluded. Values reported are medians (range). †: Mann-Whitney test.

IMAGE: images/906524_A.jpg

Fig 1. Box plots comparing various ictal parameters (A: amplitude in ì V, B: duration in sec, C: percentage of arrhythmic seizures and D: seizure frequency in Hz) of individual seizures in neonates with mild to moderate (gp I=grades 1-5, n=10) and severe (gp II=grades 6-8, n=14) abnormalities of EEG background. Only the amplitude of seizures was significantly different between the groups (Mann- Whitney U=24.5, p=0.007).

1.071

COMPUTER ASSISTED EEG MONITORING IN THE ADULT ICU

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Rationale: Computer assisted EEG interpretation in the ICU strongly assists the use of continuous EEG monitoring in critically ill patients. Its main goal is to detect, at an early stage, derangements in brain function, in particular (non-convulsive) seizure activity and ischaemia, allowing a window of opportunity for interventions.

Methods: Eight quantitative features were extracted from the raw EEG and subsequently combined into a single classifier. Features included mean power, Brain Symmetry Index, Burst-Suppression ratio and periodicity. For classification, a decision tree was used. The system was trained by using 41 EEG recordings. All EEG recordings were visually assessed by an experienced electroencephalographer. Patterns included normal, iso-electric, low voltage, burst suppression, hypofunctional, generalized periodic discharges and seizure activity. For evaluation, 20 independent EEG recordings were used. After real-time implementation of the classifier in NeuroCenter EEG (Clinical Science Systems, Netherlands), clinical evaluation in ICU patients was performed.

Results: 36 (88%) epochs of the training set and 17 (85%) epochs of the test set were classified correctly. Implementation in the NeuroCenter EEG monitor allowed real-time analysis in the ICU. The user interface presents both trend-curves and text output. At present, we have used the system in over 20 patients in our ICU. In approximately 70% of the patients, the computer interpretation showed good correspondence with the visual evaluation. In the remaining ~ 30% discrepancies were observed. Part of these were caused by artifacts, were the remainder was attributed to erroneous classification. The use of continuous EEG registrations and the real-time classification provided essential information for the clinical decision making in a substantial number of patients.

Conclusions: We present our first implementation of a real-time computer assisted interpretation of EEG patterns as observed in the ICU, based on a combination of eight features. At present, the system still underperforms as compared to an experienced electroencephalographer, with a classification accuracy of approximately 70%. At present, we are working towards a further improvement of the classifier, including the use of computer assisted analysis of video to assist in the detection of various artifacts.

IMAGE: images/905185_A.jpg

The user-interface, illustrating the classification during a 4-h EEG registration of an ICU patient. Initially, the EEG shows a hypofunctional pattern, evolving into GPDs. The interpretation displayed, is based on the last 5 minutes of the recording.

1.072

A PROBABILITY ESTIMATE FOR THE TIME TO FIRST DIAGNOSTIC EVENT DURING LONG-TERM VIDEO-EEG MONITORING

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Rationale: Long-term video EEG monitoring (LTM) is a resource intensive procedure for diagnosing and characterizing behavioral episodes and seizures, and for presurgical evaluation of medically refractory epilepsy. How long should we monitor patients to establish a diagnosis of epilepsy or psychogenic nonepileptic seizures?

Methods: We prospectively collected video EEG data from consecutive patients admitted for noninvasive LTM at the UW Regional Epilepsy Center between July 1, 1999 and June 1, 2006. We included only the initial LTM admissions, and classified any captured event as diagnostic, confirmatory, indeterminate or irrelevant, and recorded their time of occurrence relative to admission. We also coded diagnostic events as psychogenic nonepileptic, generalized, focal, or epileptic-undefined, the latter when the classification as focal or generalized could not be made. We estimated the probability of capturing a diagnostic event at different monitoring times using the product-limit (Kaplan Meier) estimator.

Results: 1453 LTM studies (59.0% female) were selected. The first captured event was diagnostic in 51.4%, indeterminate in 30.3%, and irrelevant in 5.0% of patients. 13.3% of patients did not experience any events. 69.2% of patients had at least one diagnostic event. In these studies, the first diagnostic event was preceded by indeterminate or irrelevant events (range 1-26) in 25.8%. The first diagnostic event type was psychogenic nonepileptic in 40.8%, focal in 46.0%, generalized in 13.0%, and epileptic undefined in 0.2% of patients with diagnostic events. The median length of stay was 3.92 days (range 0.17-11.92) for all patients, and 3.92 days (range 0.21-10.92) and 4.92 days (range 0.17-11.92) for patients with and without captured diagnostic events, respectively. The median time to first diagnostic event was 0.7 days (range 0.01-7.03) for psychogenic nonepileptic, 0.99 days (range 0-

7.35) for generalized, and 1.27 days (range 0.04-8.21) for focal events. The probability of capturing a diagnostic event in the average patient referred for LTM was 0.36 after 1 day, 0.5 after 47 hours, 0.6 after 3 days, 0.72 after 5 days, and 0.84 after 9 days of monitoring.

Conclusions: LTM is a useful but resource intensive tool for event diagnosis, epilepsy characterization, and presurgical evaluation. This study was the first step in providing clinicians with a probability estimate for capturing a diagnostic event during LTM. This exceeds 50% in 2 days of recording.

1.073

PREVALENCE OF CONTINUOUS EPILEPTIFORM DISCHARGES ON EEG IN PATIENTS TREATED WITH CEFEPIME AND MEROPENEM

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Rationale: Cephalosporins are among the most widely prescribed class of antibiotics in hospitals. Cefepime, with its broad spectrum activity, is one of the mostly used drugs in empirical therapy for severe infections. Studies have suggested that mortality was higher in patients treated with cefepime than in those treated with other beta-lactams. There was no good explanation for this. Several case reports of non-convulsive status epilepticus associated with cefepime in patients with renal failure suggested that neurological complications might be involved. We compared the proportion of patients associating continuous epileptiform discharges on EEG while receiving cefepime with those receiving meropenem, another broad spectrum antibiotic commonly used. The aim was to determine whether non-convulsive status was more frequent with cefepime than with meropenem. This might explain the higher mortality reported in literature.

Methods: We reviewed the databases of patients who had an EEG performed during treatment with cefepime or meropenem during the last three years. EEGs were either routine 20 to 30 minutes EEGs or continuous EEG monitoring. Clinical and biological characteristics of patients associating continuous epileptiform discharges on EEG while taking cefepime or meropenem were studied, as well as brain iconography. Proportions were compared using Fisher's exact test.

Results: We studied 933 patients treated with cefepime and 1005 patients treated with meropenem. Continuous epileptiform discharges on EEG were found in 16 patients in the cefepime group and in none in the meropenem group (1.7 vs 0%, $p< 0.001$). Fifteen patients had generalized periodic epileptiform discharges (GPEDs) and 1 continuous multifocal spikes. Among the 16 patients, 78 % were hospitalized in the intensive care unit. Mean age was 67 years. No patients were known to have epilepsy. Brain iconography showed a sequellae of a left frontal stroke in one patient and aspecific leucoencephalopathy in two others. Blood creatinine concentration was over 1 mg/dL in 6 patients and elevated liver enzymes in 5. No patient had major electrolyte disturbances. Mean time to diagnosis was 5 days (range 1 to 10) after antibiotic was started. 30 day mortality was 21%.

Conclusions: Continuous epileptiform discharges on EEG like GPEDs are not specific of non-convulsive status epilepticus (NCSE). Differential diagnosis is broad and includes common affection like hepatic and other metabolic encephalopathies as well as rare diseases like Creutzfeldt-Jakob disease. EEG findings compatible with NCSE were found only in the cefepime group. Contrary to previous series, only one third of our patients had renal impairment. Those results suggest that cefepime could be an independent risk factor for NCSE. Until a prospective study is performed to establish a formal link, in patients with altered consciousness under cefepime treatment, we recommend performing EEG (or continuous EEG monitoring if available) or shift to other antibiotics.

1.074

CHANGES IN SYMPATHETIC ACTIVITY ASSOCIATED WITH EPILEPTIC SEIZURES

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Rationale: Modulation in skin conductance, referred to as electrodermal activity (EDA), reflects purely sympathetic activity of the autonomic nervous system. Several cortical structures with recognized seizure potential have connections with autonomic centers and electrical stimulation of such structures can induce changes in EDA (Mangina CA et al. *Int J Psychophysio* 1996;22:1-8). We hypothesized that epileptic seizures can induce changes in EDA.

Methods: We continuously recorded EDA of pediatric patients with epilepsy admitted to the long-term video-telemetry monitoring unit at Children's Hospital Boston using custom designed wrist-worn EDA sensors. Video-EEG recordings were retrospectively reviewed by an epileptologist blinded to the EDA data to determine seizure semiology, ictal onset and offset times on EEG, and EEG localization. EDA recordings were low-pass filtered (1024 points, Hamming window, cutoff frequency of 3 Hz) to reduce motion artifacts. For each seizure, the resulting change in EDA amplitude (difference between response peak and response onset value) was calculated. The recovery time was calculated as the time from the response peak to the point where EDA fell below 37% of the response amplitude. EDA parameters between complex partial seizures (CPS) and secondarily generalized tonic-clonic seizures (2°GTCS) were compared using the Wilcoxon rank sum test.

Results: Eight patients (one female) between ages 7-20 years were included in this study. The total recording time analyzed from all patients was 23 days. 17 epileptic seizures (nine CPS and eight 2°GTCS) were evaluated. All seizures were associated with an increase in EDA. The EDA amplitude was significantly higher ($p < 0.01$) after 2°GTCS (18.86 ± 13.14 μS) compared to CPS (3.68 ± 4.92 μS). The EDA recovery time was also significantly longer ($p < 0.05$) after 2°GTCS (6.68 ± 6.28 min) compared to CPS (2.49 ± 1.93 min).

Conclusions: We report of spontaneous seizure-induced elevation in EDA in patients with epilepsy. Our pilot series suggests that a massive activation of the autonomic sympathetic nervous system occurs during 2°GTCS. This may be a sign of autonomic instability that may play a role in the pathophysiology of sudden, unexpected death in epilepsy. Further studies regarding the relationship between peri-ictal EDA and heart rate variability, a risk factor for sudden cardiac death, are currently underway.

Table 1. Clinical characteristics of patients with epilepsy

IMAGE: tables/907052_T1.jpg

CPS = complex partial seizure; 2°GTCS = secondarily generalized tonic-clonic seizure

IMAGE: images/907052_A.jpg

Figure 1. Comparison of peri-ictal EDA parameters between complex partial seizures (CPS) and secondarily generalized tonic-clonic seizures (2°GTCS). (a) EDA amplitude (b) EDA recovery time

1.075

QUANTITATIVE EEG TRENDING FOR MONITORING NON-CONVULSIVE SEIZURES IN ICU PATIENTS

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Rationale: Use of continuous EEG monitoring in ICU settings has been expanding rapidly. However, reliable interpretation of prolonged EEG recordings in critically ill patients requires significant expertise and is extremely time consuming, which severely limits its rapid and widespread use. As an initial step in building an accurate seizure detector for use in ICU settings, we investigated the sensitivity and specificity of quantitative EEG (qEEG) trending for rapidly identifying frequent non-convulsive seizures in ICU patients during continuous EEG monitoring.

Methods: EEG recordings recorded from five ICU patients were studied. The total duration of the EEG analyzed was about 48 hours, which contained 142 non-convulsive seizures. The qEEG trending consisted of measures of signal regularity (pattern-match regularity statistic, PMRS), amplitude variation (AV), and maximal local frequency (MLF), all calculated for each 5.12 second epoch. Since the PMRS value decreases with the increase of signal regularity, it was hypothesized that PMRS values would drop significantly during ictal activity. AV and MLF were used to reject drops of PMRS values due to rhythmic artifacts or normal physiological movements. In addition, since seizures in ICU patients vary more spatially compared to those in EMU patients, trending in multiple recording regions was calculated simultaneously. The resulting qEEG trending was analyzed to investigate how PMRS drops (at least 2 standard deviations below the mean of the preceding 60 seconds) correlated with the occurrences of non-convulsive seizures.

Results: Figure 1 demonstrates an example of PMRS trending derived from four recording regions in a 120-minute recording with 10 seizures recorded. Each drop in PMRS values coincided with a 15-20 second ictal discharge. Overall, the PMRS trending accurately detected 141 out of the 142 non-convulsive seizures (99.3% sensitivity). The single seizure missed by PMRS trending was due to the presence of an electrode artifact (high AV) during the ictal period. In addition, there was only one false positive detection during the entire 48 hours of recording.

Conclusions: These findings suggest that it is feasible to develop a robust and reliable ICU seizure monitoring system based on multi-region qEEG analysis. Application of these trending measures to a larger population of ICU EEG recordings will help further define the strengths of this novel qEEG technique.

IMAGE: images/908018_A.jpg

Fig. 1: An example of PMRS trending from four recording regions in a 120-minute recording with 10 seizures recorded.

1.076

DYSTONIC POSTURING AND DYSTONIC AUTOMATISMS IN MESIAL TEMPORAL LOBE EPILEPSY: WORSE SURGICAL OUTCOME?

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Rationale: Unilateral ictal dystonic posturing (DP) occurring in 15-70% of patients is a reliable lateralizing sign in temporal lobe epilepsy (TLE). Diagnostic criteria stringency, epilepsy etiology and mesial as opposed to lateral TLE account for the wide variability. Contralateral DP associated with ipsilateral upper limb automatisms present high lateralizing value. Unilateral ictal akinesia, “dystonic automatisms”, as RINCH (Rhythmic Ictal Nonclonic Hand) motions and nonmanipulative proximal upper extremity automatisms (NMUEAs), and ipsilateral head turning (HT) are associated symptoms, probably with similar pathophysiology. DP could be the expression of an attempt of the brain to avoid imminent generalization. Predictive value of DP in post-operative seizure-outcome remains controversial.

Methods: Four-hundred ninety-one seizures of 151 patients with unilateral mesial temporal sclerosis (MTS), who underwent temporal lobectomy at UNIFESP, with at least one year of follow up, were reviewed without knowledge of clinical data. Patients under 15 years, or with other lesions besides MTS in MRI, were excluded. Surgical outcome with respect to seizures was assessed in the first anniversary of surgery and in the last visit, according to Engel Scale. All patients gave consent for analysis of their seizures for research purposes.

Results: DP was observed in 134 seizures (27.3%) of 53 patients (35%), 90% contralateral to the operated side. The mean DP latency from ictal onset was 33.6 s, and DP mean duration was 42.2 s. Upper limb automatisms occurred in 89.5% of seizures. Ipsilateral to DP, ictal akinesia occurred in 31.5%; RINCH in 5%, and NMUEAs in 6.7%. HT occurred in 70.2%, 90% contralateral to DP. RINCH without DP occurred in 22 seizures (6.2%) of eight patients, contralateral to the operated side in 75%. NMUEAs without DP, in seven seizures (2%) of four patients, contralateral in 50%. Seventy-two seizures evolved into secondarily generalized tonic-clonic seizures (14.4%). Sixty-one of these (84.7%) were not preceded by DP, whilst only 11 of them (15.3%) occurred after DP (p=0.03). Considering all seizures with DP, 8.2% evolved into secondary generalization. Regarding seizure outcome, the mean of follow up was 45.6 months (range 12-84). At the first anniversary after surgery, 51.0% of patients without and 45.0% of those with DP were free of all seizures (Engel IA; p=0.5). At last visit, 57 patients were between two and five years of follow up. In this group, 17.5% without (p=0.008), and 22.2% with DP (p=0.63) restarted having seizures. Among patients with more than five years of follow up (n=53), 30.3% without (p=0.01) and 15.5% with DP (p=0.12), restarted having seizures.

Conclusions: Unilateral or predominantly unilateral DP occurred in 35% of patients, 90% contralateral to the operated side. RINCH and NMUEAs without DP were less frequently observed, and contralateral

to the operated side in 75% and 50%, respectively. DP was associated with a lesser probability of generalization of seizures. Finally, DP was not related to worse surgical outcome.

1.077

NEW METHOD FOR IDENTIFICATION OF RESPONSES TO SINGLE PULSE ELECTRICAL STIMULATION IN EPILEPSY PATIENTS

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Rationale: In the electrocorticography (ECoG) spike-like delayed responses, remote from the stimulus site, can be evoked with Single Pulse Electrical Stimulation (SPES). These responses are pathological and related to the epileptogenic zone. However the clinical use of SPES is compromised by the time-consuming and subjective visual analysis. In order to increase the efficiency and objectivity of SPES, we developed a method for automatic detection of evoked responses by SPES using the frequency characteristics of the responses. This method may also detect high frequency oscillations (HFOs, 80-500 Hz) as a SPES response.

Methods: Subdural ECoG data were recorded from a temporal lobe epilepsy patient evaluated for surgery. A 32 electrode channel grid and four strips (eight channels) covered the temporal lobe. SPES (10 epochs, 1ms, 8mA, 0.2Hz) was performed stimulating over adjacent electrode pairs, recorded at a 2048Hz sampling rate. A bipolar montage of adjacent electrodes was chosen. Spikes and HFOs (ripples 80-250Hz, fast ripples 250-500Hz) were marked by an experienced ECoG reader for electrodes in- and outside the seizure onset zone. We applied a wavelet based automated time-frequency analysis, computing mean event-related changes in spectral power compared to the pre-stimulus baseline power (1). The stimulus artifact was corrected by linear interpolation. Epochs were analyzed for [-1s:1s] around the stimulus. Baseline power was computed for a pre-stimulus interval [-1s:-0.2s]. The power spectra were evaluated in the frequency range 10-520Hz. Event Related Spectral Perturbation (ERSP) with respect to baseline and bootstrap significance were calculated (1). The ERSP of single epochs was evaluated for consistency within the frequency bands of spikes, ripples and fast ripples as marked by the observer. The ERSP calculated for 10 epochs was compared with the results for a non-seizure versus seizure onset zone channel.

Results: For single epochs a significant ($p<0.05$) ERSP increase (red) within the frequency range of 10-80Hz showed that matches with events marked by the observer as spikes. There is also a match for ripples and fast ripples (figure 1). Average ERSP of multiple epochs showed a significant increase in all frequency ranges in the seizure onset zone channel while only a slight increase in the spike frequency range was seen in the non-seizure onset zone channel (figure 2).

Conclusions: With this algorithm responses evoked by SPES, spikes and HFOs, could be readily identified in the ECoG. It replaces the subjectivity of visual analysis with the objectivity of frequency decomposition combined with a measure of significance. The analysis allows efficient digital processing of multiple stimuli. This new method offers a way to study the clinical meaning of SPES responses in more detail.

1.Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004; 134 (1):9-21.

IMAGE: images/905288_A.jpg

IMAGE: images/905288_B.jpg

1.078

ICTAL PATTERNS IN MESIAL TEMPORAL LOBE EPILEPSY RECORDED BY FORAMEN OVALE ELECTRODES

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Rationale: Patients with mesial temporal lobe epilepsy (MTLE) resistant to AEDs may be candidates for surgery. While scalp video-EEG often identifies the side and site of seizure onset, some patients need more investigation to distinguish the epileptogenic zone from targets of propagated activity starting in mesial areas. We have developed experience using foramen ovale electrodes (FOs) as a minimally invasive diagnostic approach in these patients. FOs provide the opportunity to record close to the mesial temporal structures, avoiding the filtering and dispersing effects of the skull. We analyzed features, prevalence and significance of patterns of ictal propagation seen with FOs.

Methods: We studied 147 seizures from 17 MTLE patients that had evaluation with FOs from 2005-2010. For each seizure we established time of 1st EEG change on FOs and on scalp, time of 1st clinical manifestation, pattern of electrographic propagation and EEG features. To analyze propagation delay (FO-scalp or FO-FO), individual seizure values for each patient were averaged to calculate a per-patient mean delay.

Results: Patients had a mean of 8.6 seizures(Range2-29).In all seizures the 1st EEG change occurred in a unilateral FO. 3 major propagation patterns were identified: Type I-Early propagation to contralateral side (FO-contralateral FO-scalp)(13.6% of seizures); Type II-Late propagation to contralateral side (FO-ipsi /contralateral scalp-contralateral FO)(33.3% of seizures); and Type III- No propagation to contralateral side (FO-ipsilateral scalp or FO only)(53.1% of seizures). 27.2 % of seizures had no clinical correlate. All seizures without clinical correlate were Type III (51.3% of the events of this type). Most seizures had a scalp signature characterized by a recognized ictal pattern or slowing, however, 4.8% of the seizures were only seen on FOs. When there was scalp signature the mean delay of initial FO-scalp propagation per-patient was 13.4s (Range2.8-24.9). 4.1% of seizures with scalp signature originated from the contralateral FO. When there was propagation from FO-scalp-FO (Type II), the mean delay per-patient was 22.8s (Range4-40.5). When direct FO-FO propagation occurred (Type I), the mean delay per patient was 8.3s (Range3-28). 5 patients had predominantly Type I seizures, 8 had >50% Type II, and 4 had >50% Type III. Ictal EEG patterns on FOs consisted of a "buzz" of beta activity in 54% of seizures, and rhythmic spike-waves in the remainder.

Conclusions: Three distinct patterns of ictal propagation can be identified using combined scalp-FOs. Most patients manifest predominance of one pattern, although many have a minority of seizures that have other routes of propagation. FO-FO propagation occurs rapidly. FO recordings sometimes clarify the lateralization, and frequently define the localization of ictal onset. In some cases FO

recordings reveal that seizures arise from mesial areas contralateral to the scalp signature, a phenomenon we have termed 'ping-pong seizures'. Seizures arising from FOs frequently have no obvious behavioral correlate, however subtle effects on cognition cannot be ruled out.

1.079

SEIZURES AND RHYTHMIC ACTIVITY DURING CONTINUOUS VIDEO EEG MONITORING IN NEWBORNS RECEIVING WHOLE BODY HYPOTHERMIA FOR MODERATE TO SEVERE ENCEPHALOPATHY

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Rationale: Hypothermia can alter eeg patterns and terminate seizures. How this will affect seizures in the neonate is unknown. We characterize seizures and rhythmic activity during whole body hypothermia.

Methods: Therapeutic whole-body hypothermia was performed in 56 infants e" 36 wks gestation transported to our hospital within 6 hrs of life with either severe acidosis or perinatal complications at birth, and who had moderate or severe encephalopathy [Shankaran et al 2005]. Infants were cooled to an esophageal temperature of 33.5°C for 72 hours, then rewarmed at 0.5°C/hr to 36.5°C. Continuous video-EEG monitoring was initiated within 24hrs of life and continued throughout cooling and rewarming. 53 patients had EEGs available for review MA & TW & TT. Medical records were reviewed for administration of anticonvulsants.

Results: 15 of 53 patients had electrographic seizures. 4/15 had received Phenobarbital prior to start of video EEG monitoring. Seizures were detected on EEG within 37 hrs of life (5-37hr). 8/15 had seizures within 24 hours of life. 13/15 had seizures within 30 hours of life.

Median seizure duration was 220 seconds with range 30-845 sec.

No de novo seizure occurred during rewarming.

In some recordings, rhythmic delta activity were noted in the same channels that subsequently would have electrographic seizures. This rhythmic activity could also have some features of a seizure such as buried spikes, sharp morphology or slight changes in morphology and frequency without the full evolution of a typical seizure. This activity was not seen when seizures were controlled for at least 24 hours.

Conclusions: Characteristics of seizures during hypothermia are similar to what has been described previously in neonates. Certain rhythmic patterns can be seen in association with seizures. Further research is needed to determine whether treatment of particular types of rhythmic activity improves clinical outcome.

1.080

SHORT-TERM OUTCOME PREDICTION BY ELECTROENCEPHALOGRAPHIC FEATURES IN CHILDREN TREATED WITH THERAPEUTIC HYPOTHERMIA AFTER CARDIAC ARREST

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Rationale: Electroencephalographic (EEG) features may provide objective data regarding prognosis in children resuscitated from cardiac arrest (CA), but therapeutic hypothermia (TH) may impact its predictive value. We aimed to determine whether specific EEG features were predictive of short term outcome in children treated with TH after CA, both during hypothermia and after return to normothermia.

Methods: Thirty-five children managed with a standard clinical TH algorithm after CA were prospectively enrolled. EEG recordings were scored in a standardized manner and categorized. EEG category 1 consisted of continuous and reactive tracings. EEG category 2 consisted of continuous but unreactive tracings. EEG category 3 included those with any degree of discontinuity, burst suppression, or lack of cerebral activity. The primary outcome was unfavorable short-term outcome defined as Pediatric Cerebral Performance Category score of 4-6 (severe disability, vegetative, death) at hospital discharge. Univariate analyses of the association between EEG category and outcome were performed using logistic regression.

Results: For tracings obtained during hypothermia, patients with EEG scores of 2 or 3 were far more likely to have poor outcome than those with a score of 1 (OR 10.7, p=0.023; and OR 35, p=0.004, respectively). Similarly, for tracings obtained during normothermia, patients with EEG scores of 2 or 3 were far more likely to have poor outcomes than those with a score of 1 (OR 27, p= 0.006; and OR 18, p = 0.02, respectively).

Conclusions: A simple EEG classification scheme has predictive value in children undergoing TH after CA.

1.081

USE OF INTERICTAL HIGH FREQUENCY OSCILLATIONS AS A PREDICTOR IN THE IDENTIFICATION OF SEIZURE ONSET ZONE IN PATIENTS WITH FOCAL EPILEPSY

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Rationale: Interictal high frequency (80-600Hz) oscillations (iiHFO) have been described during invasive VEEG evaluations of patients with refractory focal epilepsy. Prior studies have demonstrated that iiHFO >250Hz are able to predict the location of the seizure onset zone (SOZ). The objective of this study is to establish if the presence and location of iiHFOs obtained with subdural macroelectrodes and frequencies 80-200Hz are useful in predicting the location of the seizure onset zone (SOZ) and post operative outcome in patients with focal epilepsy.

Methods: All patients who underwent invasive EEG evaluation at our institution between 2007 and 2009 were identified. We performed a retrospective review of EEG data as well as chart data. iiHFOs were identified and localized to the specific electrodes. The SOZ was also identified. Sampling rate was 250Hz for one of the cases and 500Hz for the rest. The time between surgery and last follow up was 6 to 31 months. The concordance between the location of iiHFOs and the SOZ was analyzed in relation to the epilepsy type and post surgical outcome (Engel Classification).

Results: 30 patients underwent Invasive VEEG evaluation at our institution between 2007 and 2009. 12 patients were excluded because of unreliable EEG data or because the source of the ictal activity was found to be non localizable. 10 (56%) of the 18 patients analyzed were female. Age range was 14-56 years. iiHFOs in a range of 83 to 134Hz were identified in 16 (89%) patients. One patient did not have resective surgery following the evaluation.

11 patients underwent temporal lobe resections, 9 of them had class I outcome at the time of last follow up. 5 of these patients had positive correlation between the location of iiHFO and SOZ. Two temporal lobe patients had outcome class II or III, one had positive iiHFO-SOZ correlation. 10 out of the 11 temporal cases had areas displaying iiHFOs outside of the SOZ.

Six patients underwent extratemporal resections. Three had class I outcome, none of them showed positive iiHFO-SOZ correlation. From the remaining 3 patients with outcome class II or III all had positive iiHFO-SOZ correlation. All of the extratemporal cases had areas with iiHFO outside of the SOZ.

Conclusions: iiHFOs in the range of 80-200Hz can be identified during VEEG evaluations using subdural macroelectrodes and sampling frequencies of 500Hz. In contrast to prior published data we did not find the presence of iiHFOs to be restricted to the epileptogenic zone as we did not find that a higher iiHFO-SOZ correlation was reflected on better postsurgical outcome both for temporal and extratemporal cases. We did not find the presence of iiHFO outside of the SOZ to be related with worse outcome in either group.

iiHFOs in the range of 80-200 might not be as useful as faster iiHFOs (>250Hz) in identifying the epileptogenic zone.

1.082

TIME TO FIRST EPILEPTIFORM DISCHARGE IN AN EPILEPSY MONITORING UNIT

Madeline Fields and L. V. Marcuse (Neurololgy, Mount Sinai Hospital, NY, NY)

Rationale: Currently scant data exist on the time necessary to detect epileptiform discharges in patients being monitored in epilepsy monitoring units (EMUs).

Methods: Twenty five consecutive electroencephalograms (EEGs) recorded in the EMU were selected during a one month period. EEGs were included regardless of age, sex or reason for admission. Two epileptologists as well as automated spike detectors were used to review the EEGs in their entirety. The first epileptiform discharge was identified and confirmed in a blinded fashion.

Results: Forty-eight percent (12/25) of the EMU studies showed no epileptiform discharges. In 56% (14/25), epileptiform discharges were detected during the course of the study. Of those that showed epileptiform abnormalities, 14% (2/14) demonstrated spikes/ sharp waves after more than 1 hour of recording. Whereas in 86% (12/14), epileptiform abnomralities were seen in less than 15 minutes of recording time.

Conclusions: Epileptiform abnormalities most often declare themselves within the first 15 minutes of a recording. However, occasionally epileptiform discharges do not appear until well into an EEG recording.

1.083

EEG MONITORING DURING INTRACRANIAL SURGERY FOR MOYAMOYA DISEASE

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Rationale: Moyamoya disease, a condition predisposing affected individuals to strokes secondary to pathological narrowing of the intracranial internal carotid arteries and their branches, can be successfully treated with surgical revascularization of the brain. One of the major risks of surgical treatment is intraoperative stroke, yet there remains no commonly accepted method to monitor for ischemic changes during the procedure. Interestingly, there is extensive experience with the use of intraoperative electroencephalography (EEG) to monitor for cerebral ischemia during carotid endarterectomy, an operation done for atherosclerotic disease of the carotid artery in the neck. Recognizing the potential utility of this technique in moyamoya surgery, our institution has routinely used intraoperative EEG monitoring during moyamoya operations since 1994, using modified EEG montages to accommodate for the craniotomy incisions. Here we report on our experience with this technique.

Methods: The case records and intraoperative EEG recordings of all patients (n=220 patients undergoing 398 craniotomies) treated with surgical revascularization for moyamoya (pial synagiosis) disease performed over a 14 year period (1994-2008) were reviewed.

Results: EEG slowing occurred in 100 cases (45.5%) and was persistent in 9 cases (9%). Slowing coincided with specific operative manipulations, most commonly during suturing the donor vessel to the pia, and at the time of closure of the craniotomy. Slowing generally occurred bilaterally and was independent of the side of intervention. The presence, length, and severity of observed EEG slowing was not predictive of perioperative ischemic events

Conclusions: This study demonstrates that intraoperative EEG recording using modified EEG montage is technically feasible, even with bilateral craniotomies. While not predictive of perioperative ischemic events in this series, EEG changes could be correlated with specific operative interventions and interestingly revealed global responses to unilateral manipulation. These findings suggest that prospective analysis of this technique may elucidate additional methods of predicting - and possibly preventing - perioperative ischemic events.

1.084

SIGNIFICANCE OF DECREMENT IN INTRACRANIAL EEG INTERPRETATION FOR LOCALIZATION OF THE EPILEPTOGENIC ZONE IN RESECTIVE SURGERY

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Rationale: Determination of epileptogenic zone in planned resective surgery for focal onset seizures can be difficult. Typically spike and wave activity and fast beta activity are considered the primary features for localization of seizure onset in intracranial EEG monitoring. With the extensive use of subdural electrodes, there have been reports of electro-decrement in certain regions of the grids seen prior to the onset of the spike and wave complexes or beta activity. Our results show that attention to the region of the onset of electro-decrement can aid in determining the extent of the epileptic zone.

Methods: A review was done of the intracranial EEG monitoring findings in 4 patients who presented for resective surgery, ages 4- 19. In all of these patients, electro-decrement occurred just before spike and wave complexes or fast beta activity.

Results: The localization of the decrement aided in the determination of the epileptogenic zone and the extent of resection. In two patients, the extent of resection of epileptogenic zone in the first surgeries did not take into account the entire extent of the decrement prior to the spike onset. These two patients underwent 2nd surgeries with Engel 1A and 1D outcomes.* The other two patients achieved Engel 1A outcome after the initial resection. Of the two who underwent one resection, one had a right fronto-temporal resection, one underwent right medial-frontal resection. The other two were left temporal resections with subsequent extension of previous surgery.* seizures with fever/illness only & neurocutaneous disorder

Conclusions: Spike and fast beta bursts (buzz) are not the only important factors in determining the seizure onset zone or epileptogenic zone in epilepsy surgery. Decrement on intracranial monitoring is a useful marker for seizure onset and determination of the epileptogenic zone, frequently suggesting either a larger zone or deeper focus, thereby aiding in surgical planning.

1.085

EPILEPTIFORM ACTIVITIES IN CONTINUOUS EEG MONITORING DURING THERAPEUTIC HYPOTHERMIA

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Rationale: Hypothermia has been recognized as standard treatment after cardiac arrest. There are few data about the significance of findings in continuous EEG monitoring during therapeutic hypothermia.

Methods: We performed a retrospective analysis on all patients that underwent therapeutic hypothermia after cardiac arrest. We reviewed data from January 2008 to December 2009. Every patient underwent continuous EEG monitoring. Board certified neurophysiologists interpreted EEG. Initial pattern of EEG background activity, latency of first epileptiform activity, latency of electrographic seizure and the prognosis were analyzed. Prognosis, at the time of discharge, was classified by utilizing Glasgow-Pittsburgh cerebral performance categories (CPC), dividing performance into five categories (1: conscious and alert with a normal function or slight disabilities, 2: conscious and alert with the moderate disabilities, 3: conscious with the severe disabilities, 4: comatose or persistent vegetative state, 5: brain death or death from other causes). Multiple comparison statistical analysis was performed using Tukey-Kramer Procedure.

Results: A total of 26 patients (14 men and 12 women) were involved. All of patients were treated with standard protocol of therapeutic hypothermia, in which target body temperature of 32 degrees Celsius for initial 24 hours followed by gradual warming for next 24 hours. The mean age was 60.3 years, ranging from 32 to 87 with standard deviation (SD) of 17.5. Mean duration of monitoring was 86.8 hours, ranging from 4.9 to 381.1 hours with SD of 70.0. Initial EEG background was the severe diffuse suppression in 10 patients, suppression-burst pattern in 4 patients, alpha or theta coma pattern in 3 patients, generalized slow wave in 5 patients and generalized periodic epileptiform discharges (GPEDs) in 4 patients. Epileptiform activity was found in 12 patients (46.2%). Generalized spike or sharp wave in suppression-burst pattern was found in 9 patients, GPEDs were found in 7 patients. Tri- or diphasic sharp wave transients were found in 2 patients. Focal spike or sharp wave activity was found in 1 patient. Mean latency of 1st epileptiform activity onset was 17 hours 47 minutes (ranging from 0 to 87 hours 50 minutes).

Electrographic seizures were recorded in 2 patients (7.7%). Both were generalized seizure arising from the background of suppression-burst pattern. Mean latency of 1st seizure onset was 11 hours 58 minutes (ranging from 2 hours 30 minutes to 21 hours 26 minutes). 21 patients had a CPC score of 5, 1 patient had 4, 2 patients had 3, none had 2 and 2 patients had 1.

An initial background with the generalized slow wave was correlated with better prognosis compared with other types of background activity ($p=0.017$). The presence of epileptiform activity did not correlate with the prognosis.

Conclusions: The majority of patients (21 of 26) failed to survive despite hypothermia. Continuous EEG background with generalized slow wave activity, but not epileptiform activity, correlated with survival in this study.

1.086

SPATIAL AND TEMPORAL RELATIONSHIP OF HFO AND INTERICTAL SPIKES IN PATIENTS WITH MEDICALLY REFRACTORY NON-LESIONAL EPILEPSY

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Rationale: High frequency oscillations (HFO) called ripples(80-250Hz) and fast ripples (250-500Hz) can be recorded from intracranial EEG(IC-EEG) macroelectrodes in patients with intractable epilepsy. We analyze various correlations of interictal HFO and spike in order to understand their relationship to each other and to the epileptogenic zone.

Methods: We studied 10 subjects with refractory localization-related epilepsy without clear lesion on neuroimaging studies who underwent 2-stage surgery with subdural grid/depth electrode placement(80 to 124 electrodes per patient). Three 10-minute interictal EEG samples (one sample per 24-hours, roughly at the same time of the day and during awake, resting phase) at least six hours from the last ictus were analyzed. Each file was reviewed and manually corrected by a single EEGer. Each electrode was labeled by its ictal activity as “seizure onset” (SO) (electrographic involvement at the earliest point in seizure), “seizure spread” (SS) (EEG involvement within 10 seconds of seizure onset), or “neither” (N). Seizure onset and spread are defined as epileptogenic zone.

EEG was sampled at 200 or 1000Hz and HFO were recorded by using high pass filter at 50Hz. Automatic computer program analysis was performed in Matlab (MathWorks) to calculate the occurence frequency

of HFOs and spikes per electrode. Two hundred milliseconds of data were searched on either side of a marked HFO to look for co-occurrence of spike. Analysis included comparing the frequency of HFO occurrence, spike frequency, and frequency of HFOs with concurrent spikes, to each electrode based on designation as ictal onset, spread, or neither.

Statistical analyses included ranked data correlations, ANOVAs with subject as a blocking factor to reduce the error term, followed by post-hoc Tukey tests as appropriate. Alpha was set at $p < .01$.

Results: Total average spike frequency per patient was calculated as 9,390 and total average frequency of HFO per patient was 13,073. Rank score correlation of frequency of spikes and HFO is 0.60. Correlation of frequency of HFO with concomitant spikes within +/- 200ms of a marked HFO was .69. The ANOVA was significant for spikes, with post-hoc tests showing onset zone was significantly different (higher) than spread or neither. HFO was significant with onset being different (higher) than neither. HFO with a spike was significant, with onset being higher than spread or neither.

Conclusions: We hypothesize that electrode with high spiking frequency also had high HFO frequency at the seizure onset and spread zone. Correlation of HFO and concomitant spike was statistically significant therefore we assume that there is a good probability for some of the HFO to be associated with spikes. These preliminary results suggest that interictal spike frequency and frequency of HFO occurrence both can discriminate between the epileptogenic zone from the surrounding brain area.

1.087

CLINICAL INDICATIONS AND DIAGNOSTIC USEFULNESS OF PROLONGED VIDEO ELECTROENCEPHALOGRAM (VEEG) MONITORING

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Rationale: To identify patients most likely to have clinical seizures, as well as those with more subtle presentations (i.e., altered mental status, behavioral changes) documented on continous VEEG monitoring.

Methods: Two hundred and fifty patients who underwent VEEGs were studied retrospectively out of the total of three hundred seventy-one VEEG admissions during the study period of one year in pediatric neurology at the Children's Hospital of NJ at Newark Beth Israel Medical Center. All VEEG obtained in 2009 on patients under 18 years were reviewed; no exclusion criteria (no patients were disqualified if data was in records). The total number of monitoring days was seven hundred thirty-seven and the length of stay was approximately 48 hours. The common indications for VEEG during the study period were: 1) New onset unprovoked events, 2) Status epilepticus/altered mental status, 3) Classification of seizures and epileptic syndrome, 4) Adjustment of treatment /new treatment with anti-epileptic drugs(AED), 5) Response to treatment/quantification of seizures, and 6) Withdrawal of medications (AEDs).

Results: Of the 250 patients studied 100 were reported normal(40%). Abnormal background was seen in 86(34.6%). Seizures were noted in 82(32.8%) and 77(30.8%) were non-epileptic.

Conclusions: VEEG monitoring is very important to diagnose epilepsy correctly, along with type of seizure and epileptic syndromes as early as possible, especially non-convulsive seizures as the excessive demand and increased blood flow associated with ictal activity may further compromise at-risk brain tissue following acute brain insult. Also it is important to differentiate non-epileptic events (e.g., in our study there were 30%) and treat them appropiately to avoid unnecessary exposure to anti-epileptic drugs(AED).

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IMAGE: images/906625_B.jpg

1.088

TOPOGRAPHY OF SLEEP MORPHOLOGY IN PATIENTS WITH INTRACRANIAL ELECTRODES

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Rationale: To describe sleep structures and localize their intracranial generators on subdural electrodes (SDE) during monitoring for epilepsy surgery. Analysis of sleep structures including spindles, V-waves, K-complexes, as recognized on simultaneous scalp and SDE recordings

Methods: K complexes, Spindles and Vertex waves on Cz surface recordings were correlated with areas of the cortex on implanted electrodes. Maximum amplitude was assessed using the contra-lateral ear electrode as reference. Sleep architecture was defined according to the AASM Manual for the Scoring of Sleep and Associated Events. Fifteen of the sleep elements each were analyzed per patient. SDE localization was divided as: perirolandic (superior, middle and inferior pre and post-central area); frontal (lateral, mesial, anterior, orbito-frontal), parietal, occipital and temporal (lateral, mesial, basal) coverage. The electrode location was confirmed in seven patients using MRI 3D reconstruction and in the remaining seven patients by 3D CT reconstruction

Results: Fourteen patients, ages of 3 to 21 years (mean 11.4years; 8 males) were analyzed. Twelve patients had SDE placement involving the perirolandic area, one had exclusively temporal coverage and one had posterior SDE. The etiology of the epilepsy included developmental lesions in six, recognized acquired lesions in five and unknown mechanism in three. Spindles were visualized maximally in the central peri-sulcal region, but also seen in the frontal regions, including the mesial areas. Vertex waves and K complex were also seen maximally in the perirolandic area with field in the anterior regions. They were not seen in electrodes representing the hippocampus and mesial temporal areas. Cortical surface location in patients with MRI 3D reconstruction included: spindles and vertex waves in the middle frontal gyrus (n=2), precentral gyrus (n=2) and post-central gyrus (n=1). K complexes were seen in the middle frontal gyrus (n=1) and in the pre-central gyrus (n=4).

Conclusions: This study provides the first description of sleep architecture using SDE coverage. Results have to interpreted in the setting of SDE location. Neuronal generators related to different sleep components have different locations and our preliminary data shows that there is a good cortical representation of sleep architecture correlating with traditional scalp electrodes.

1.089

ASYMMETRY OF SCALP EMG IN THE LATERALIZATION OF FOCAL EPILEPSY

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Rationale: It is not uncommon for scalp ictal EEG changes to be nonlateralizing in the setting of focal epilepsy diagnosed unambiguously on alternative grounds. We describe three patients with nonlateralizing scalp ictal EEG, in whom the pattern of EMG artifact correctly implicated the hemisphere of seizure onset as contralateral to the side of greater artifact.

Methods: Retrospective review of video-EEG (VEEG) monitoring data on three patients.

Results: 1) A 30 year old woman with left neocortical temporal lobe epilepsy experienced two generalized seizures with nonlateralizing semiology and diffuse ictal EEG. The early phase of the latter showed more abundant right sided EMG artifact. Brain MRI showed left temporal pole encephalomalacia; interictal spikes were maximum over the left midtemporal region. 2) A 42 year old man with left frontal lobe epilepsy had two generalized seizures preceded by versive rightward head deviation. Ictal EEG was nonlateralizing, though EMG artifact in the early phase was higher over the right. Brain MRI showed bilateral orbitofrontal encephalomalacia with extensive gliotic change on the left; interictal epileptiform was bilateral though higher on the left. 3) A 45-year old woman with left neocortical temporal lobe epilepsy had three secondarily generalized seizures with poor ictal EEG localization. EMG artifact was higher over the right in the initial phase of the motor seizure. Brain MRI was nonlesional; interictal epileptiform activity was restricted to the left temporal region. All three patients proceeded to invasive monitoring with subdural grid electrodes. Intracranial EEG confirmed the ictal onset zone over the left neocortical temporal, left orbitofrontal, and left anterior temporal regions respectively.

Conclusions: EMG artifact on scalp EEG, normally ignored as a contaminant, is prominent in convulsive seizures. Its asymmetry in the early phase of motor seizures, implying subtle asymmetry of tonic posturing, may provide valuable lateralizing information when the ictal EEG is itself uninformative. When seizure semiology is also nonlateralizing, asymmetric EMG may be the only VEEG observable that points to the hemisphere of ictal onset. A larger study is under way to confirm these pilot observations.

1.090

THE RELATIONSHIP OF ICTAL EEG BETWEEN DEPTH AND SUBDURAL ELECTRODES IN MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: In mesial temporal lobe epilepsy, the intracranial depth EEG patterns have been investigated in relation to surgical prognosis and to pathological findings of hippocampal sclerosis. Studies about intracranial EEG using subdural electrodes usually have been performed regarding to lateralization of temporal lobe epilepsy foci. However, it has not been elucidated yet the relationship between ictal onset patterns of depth electrodes and those of subdural electrodes and the relationship between the range of ictal onset area and the location of intracranial electrodes. The aim of this study was to investigate ictal EEG patterns on subdural electrodes corresponded to ictal EEG on depth electrodes and to analyze whether the position of medial subdural electrodes and depth electrodes has influence on the range of the onset patterns.

Methods: We reviewed total 120 seizures recorded by bilateral hippocampal depth electrodes and medial and lateral temporal subdural electrodes in 20 medically intractable mesial temporal lobe epilepsy patients who underwent anterior temporal lobectomy. All patients had hippocampal sclerosis confirmed pathologically, and had been seizure free in more than two years after operation. The ictal depth EEG patterns categorized into the following four types; low voltage fast activity (LVFA), fast strain (FS), rhythmic activity (RA), and electrodecremental pattern (ED). We identified the ictal subdural EEG patterns corresponded to the ictal depth EEG patterns. The positions of depth and subdural electrodes were measured by using the brain CT image after intracranial electrodes insertion surgery. We examined whether there was positional difference of the medial subdural electrodes between patients group with only ictal depth EEG and patients group with synchronized ictal EEG on both electrodes.

Results: We observed that LVFA on depth electrodes, the most common intracranial ictal EEG pattern, was well corresponded to LVFA or ED pattern on subdural electrodes, FS corresponded to LVFA on subdural electrodes and RA and ED patterns as each RA and ED patterns on subdural ictal EEG. The 3-dimensional distance of medial subdural electrodes from the hippocampus in patients group with only ictal onset on depth EEG was significantly farther than that in patients group with synchronized ictal EEG onset on both electrodes.

Conclusions: We suggest that the ictal subdural EEG patterns were well corresponded to the ictal depth EEG patterns in the mesial temporal lobe epilepsy with hippocampal sclerosis. The distance of medial subdural electrodes from the hippocampus influences on the range of ictal onset area defined by intracranial electrodes such as depth electrodes and subdural electrodes.

1.091

DAY/NIGHT AND SLEEP/WAKE PATTERNS OF PEDIATRIC GENERALIZED SEIZURES

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Rationale: Sleep can affect seizure frequency and presentation, and epilepsy can disrupt the sleep-wake cycle and sleep architecture. There is some data on relationship of sleep to specific epilepsy types, but no data on the relationship of seizures with generalized semiology to diurnal rhythms, especially in children. The aim of this study was to evaluate the relationship of sleep/wake and day/night patterns to generalized EEG seizures.

Methods: Charts of 1044 consecutive pediatric epilepsy patients undergoing Video-EEG monitoring (V-EEG) over five years were reviewed: 967 patients were excluded due to focal epilepsy (556), non-epileptic recorded events (217), missing data (125), age over 21 years

(59) and no recorded events or seizures (10). Seizure semiology recorded during V-EEG was classified according to the ILAE seizure semiology terminology, and presence of generalized onset of seizures on EEG, and analyzed based on occurrence during day (6am to 6pm) or night and on their relationship to wakefulness and sleep, with calculated occurrence in 3-hour time blocks throughout 24 hours. Statistical analysis analysis was performed with binomial testing.

Results: Three-hundred-and-sixteen generalized seizures were analyzed in 77 children. Mean age was 6.4 years ± 5.4 (range 0-20 years), including 50.6% girls.

Tonic and tonic-clonic seizures were more frequently seen in sleep, whereas all other semiologically generalized seizure types occurred more frequently out of wakefulness.

Generalized clonic seizures had two peaks: (6-9am) and (noon-3pm) in wakefulness. Absence seizures occurred predominantly in wakefulness, (9am-noon & 6pm-midnight). Atonic seizures occurred predominantly in wakefulness (noon-6pm). Myoclonic seizures occurred in wakefulness (6am-noon). Epileptic spasms had two peaks: (6-9am and 3pm-6pm) in wakefulness.

Conclusions: Sleep and wakefulness, as well as time of day/night, are important considerations in proper characterization of generalized seizure-types. Characterization of individual diurnal seizure pattern may offer exciting new possibilities, including sleep/wake pattern variability, EEG or Video-EEG scheduling, and differential (day/night) medication dosing.

1.092

HAND STEREOTYPIES, PARTIAL MOTOR SEIZURES OR GIANT EVOKED POTENTIALS- A NEWLY DESCRIBED PHENOMENA IN RETT SYNDROME

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Rationale: Hand stereotypies is a necessary criteria for Rett syndrome diagnosis, stereotypies are usually midline although can be asymmetric and include, washing, rubbing, tapping and other. Seizures of various types including simple motor seizures are described in more than 70% of patients and focal and generalized epileptiform activity is even more common. We are describing and discussing a new observation of a "movement disorder" in Rett syndrome patients which on first glance was considered as stereotypy but because of its unique character and synchronous abnormal EEG correlate have to be differently defined. Further analysis of this phenomenon components may shed light on the origin of stereotypies in Rett syndrome

Methods: In our national Rett syndrome clinic that follows more than 150 patients we have identified 4 girls with this "unique" phenomenon. Clinical and video EEG features with specific observer manipulation of these 4 girls with typical and atypical (preserved speech variant) Rett syndrome is presented and reviewed

Results: In 4 girls with MECP2 mutation proven Rett syndrome we have noticed very frequent episodes of awake unilateral hand tapping which appears only when touching surface and completely disappear by gentle hand holding or removing hand from surface. This behavior was found to be synchronous with onset and arrest of contra lateral central spikes on EEG during V-EEG recording, did not respond to acute or chronic anti convulsant treatment and partially remitted spontaneously after few months.

Conclusions: The phenomena described and analyzed is unique and was never described before. It is not fully consistent with stereotypy neither with reflex motor seizure.EEG features may also be considered as giant evoked potentials. Its analysis may shed some light on the pathophysiology of the still unexplained hand stereotypies in Rett syndrome.

1.093

DETECTION OF MULTIPLE, SINGLE UNIT ACTIVITY FROM CONTINUOUS, LONG-DURATION, HIGH-FREQUENCY RECORDINGS IN PATIENTS WITH EPILEPSY

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Rationale: Wide bandwidth recordings (>100 Hz) have opened new opportunities for understanding the mechanisms underlying epilepsy. In addition to prior observations of pathological, high-frequency oscillations and microseizures in humans, pathological unit activity in animal models of epilepsy has been associated with seizure onset and holds promise for aiding seizure prediction. Recent advances in both acquisition and storage technology now make it feasible to record continuously at sampling frequencies (>20 kHz) sufficient to isolate the action potentials of single neurons ("unit spikes") from multiple electrodes for days at a time.

Methods: Continuous data sampled at 32 kHz were collected from multiple, microelectrodes (diameter ~ 40 μm) from patients with epilepsy undergoing evaluation for resective surgery. Unit activity was detected offline by identifying peak voltages greater than 3 standard deviations above the mean (with a minimum peak amplitude of 10 μV). These detections were further restricted by matching to a generalized template for action potentials. Periods of movement-related artifact and seizure onset times were identified by visual inspection, and were stored along with unit activity detections to a relational database system.

Results: Data were collected from 8 MTLE patients implanted with hybrid depth electrodes, which contained a total of 298 microwires in addition to standard clinical contacts. Over a total of 88.1 hours of recording, a total of 24 spontaneous seizures were recorded.

Conclusions: The amount and variability of data recorded from microelectrodes across multiple days provides a novel set of challenges for identifying unit activity compared to more common unit activity studies, in which recordings last a few hours. The ratio of the number of detections observed on an electrode compared to the average RMS of that same electrode proved a useful method for the automated identification of bad (i.e., "noisy") electrodes from more suitable candidates for the detection of unit activity. The identification of nearly simultaneous detections on multiple channels recorded in parallel is also an effective method for removing artifactual detections.

1.094

EPILEPTIC RIPPLE OSCILLATIONS IN INTRAOPERATIVE ECOG

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Rationale: An increasing number of studies suggest that high frequency oscillations (HFO) in the ripple (80-250Hz) and fast ripple band (250-500Hz) may represent surrogate markers of epileptogenic processes. HFO are investigated using invasive EEG recordings during evaluation for epilepsy surgery. Results are used for preoperative focus localization and determination of resection volumes. However, studies investigating HFO detection during the surgical procedure, i.e. in general anaesthesia in human, are lacking. Our study aims to demonstrate existence of intraoperative epileptic ripple HFO and to evaluate the correlation to hippocampal pathologies.

Methods: Electrocorticographic data (ECoG) from 15 patients with pharmacoresistant temporal lobe epilepsy were analyzed retrospectively: 9 with hippocampal sclerosis (HS) verified by histology and 1 with mesial ganglioglioma (group 1) versus 6 with no or unspecific hippocampal changes (atrophy/gliosis) (group 2). Data were recorded intraoperatively before resection using subdural electrodes: 3 temporobasal strips(4 contacts each), 1 hippocampal strip (4 contacts) and 20 electrodes over temporolateral areas. In three patients, an additional amygdala electrode (4 contacts) was used.

Data was acquired with a sample rate of 1024Hz after application of an analogue highpass filter (0.08Hz) using an IT-med amplifier (Usingen, Germany). Raw data were processed according to the short time line length method described by Gardner et al. (Clin Neurophysiol. 2007; 118(5): 1134-1143), however with the baseline noise level calculated from a user specified segment containing no detectible artefacts or ripple activity. For comparison of resulting ripple rates, spikes were detected using a visually controlled template search procedure.

Results: Ripple activity was observed in all patients, however rates of >0.5 ripples/second were achieved only in 13 of all 15 patients. In 14 patients, electrode with maximum ripple rate was located over resected volumes, however no association with a particularly good or bad outcome was seen. Ripples occured superimposed on and independent of spikes. Total rate of ripples and spikes were highly correlated ($r=0.91$, $p<0.0001$, pearson correlation). No difference between the groups was observed in regard to total rate of spikes ($p=0.51$, ranksum test). However, total ripple rate was higher in group 1: 0.24/s (0.13/s-0.40/s) vs. 0.08/s (0.01/s-0.11/s) ($p=0.055$, ranksum test). Furthermore, a significant difference in hippocampal ripple rates ($p<0.005$, ranksum test) was observed between groups: 0.03/s (0.02/s-0.17/s, 1st and 3rd quartile) vs. 0/s (0/s-0.002/s).

Conclusions: Epileptic ripples can be detected intraoperatively during general anaesthesia and occur more frequently but not exclusively in patients with specific hippocampal pathologies compared to unspecific atrophy and gliosis.

1.095

CONTINUOUS VIDEO EEG MONITORING FOR PATIENTS WITH ACUTE ENCEPHALOPATHY IN A PEDIATRIC INTENSIVE CARE UNIT (PICU)

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Rationale: The occurrence of non-convulsive seizures (NCS) in patients with coma or altered consciousness monitored with EEG is estimated at 7% to 44%. There is no consensus regarding the duration of EEG monitoring necessary to capture NCS. We aimed to provide a framework to optimize selection of patients in whom continuous EEG monitoring to detect NCS would be beneficial.

Methods: We collected data from a prospective database obtained from 96 consecutive patients, age 30 days to 18 years, admitted to the PICU at Children's National Medical Center (CNMC) between June 1, 2009 and June 1, 2010 with an acute encephalopathy and Glasgow coma scale (GCS) < 12, not explained by pharmacological sedation alone and/or baseline chronic encephalopathy. Patients were monitored continuously for 48 hours with video EEG. Monitoring was considered adequate if e" 36 hours of EEG data were collected in a 48 hour period, or if the study was discontinued due to improved mental status.

Results: 89 of 96 patients identified had adequate EEG monitoring data. Mean age was 6.7 years. 60 (63%) had an acute brain injury (anoxia, trauma, stroke, hypertensive encephalopathy, or infection). 43 (45%) had a prior neurological diagnosis, including 32 (33%) with a prior history of seizure. 49 (51%) presented with a convulsive seizure. 29 (30%) had seizures captured on EEG: 21 (72%) of these had an acute brain injury, 8 (28%) had a history of seizure, and 20 (69%) presented with a convulsive seizure prior to EEG. During EEG monitoring 21 (72%) had NCS only and 8 (28%) had both convulsive and NCS. No patients had convulsive seizures alone. Recurrent seizures on EEG were seen in 24 (83%). The first seizure of the EEG recording occurred within 30 minutes in 10 (34%), 30 minutes to 24 hours in 11 (38%), and between 24 and 48 hours in 5 (17%).

Conclusions: NCS are common in children who present with an acute encephalopathy and GCS < 12. Nearly all patients with seizures detected on EEG had a history of seizures, presented with a seizure prior to EEG placement, or were diagnosed with an acute brain injury. Our data supports prior studies demonstrating that the majority of patients with seizures detected on EEG will have a seizure in the first 24 hours of monitoring, though over one quarter may require > 24 hours of monitoring in order to detect the first seizure. The high yield of seizure detection, most of which are NCS, supports the practice of continuous video EEG monitoring for at least 24 hours in this population.

1.096

ANALYSIS OF CONTINUOUS ELECTROENCEPHALOGRAPHY IN THE INTENSIVE CARE UNIT FOR NONCONVULSIVE SEIZURE ACTIVITY- A COMPARISON OF FOUR METHODS

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Rationale: Nonconvulsive seizures (NCS) are more prevalent in the ICU than previously thought, and Continuous Electroencephalography (CEEG) is increasingly employed to detect and respond to them. Collecting CEEG digitally generates copious data, and the most efficient way to review it is unknown. Complete review by an encephalographer is the gold standard but is time consuming. Other methods include automatic seizure detection algorithms which are included most CEEG programs, scheduled review (i.e., review 5 out of every 30 minutes), and Compressed Spectral Array (CSA). The purpose of this investigation was to compare the sensitivity, specificity, and positive

predictive value (PPV) of these methods using complete review as the gold standard.

Methods: Nine patients were identified with NCS (patients who had clinically obvious events were excluded) who were monitored in 3 New York State ICU's since 2009. Synchronized digital video and digital EEG (Ceegraph Vision, version: 7.03.06) with International 10-20 system was used. The indication for all was altered mental status. A 24 hour period with at least 1 NCS was selected. Comprehensive review was performed by an electroencephalographer, and seizure onset and offset times were recorded. Automated seizure detection was performed with the following parameters: Amplitude Threshold: 2.7, Detection Threshold: 1, Min. Frequency: 3, Max Frequency of Variation: 40. The CEEG was reanalyzed using only the first 5 minutes of each 30 minutes of the selected 24 hour period. FFT frequency analysis will be used to generate a spectrogram, and then another encephalographer who is blinded to the location of seizures will review the spectrograms and identify peaks of interest. Peaks which include seizure activity 2.5 minutes before or after them will be considered positive. True positive, true negative, false positive, and false negative rates are calculated.

Results: The mean age was 55 years (3 days to 81 years). Etiology was unknown in 4 cases, post-anoxic in 3 cases, and ICH in 2 cases. The mean seizures per patient/day was 9.4 (1-16). Most seizures lasted approximately 60 seconds with the longest lasting over 120 minutes. For some, there were multiple scheduled reviews or automatic detections. The sensitivity, specificity, and PPV of the seizure detection algorithm were 86%, 99%, and 84%. The sensitivity, specificity, and PPV of scheduled review were 27%, 97%, and 5%. CSA analysis is ongoing.

Conclusions: This investigation indicates that relying on automatic seizure detection or scheduled review alone will result in missing a significant number of NCS in the ICU, and as a consequence, may lead to incorrect therapeutic decision-making. The yield of scheduled review in particular is very low. These early results suggest that complete review of CEEG data should be performed. Future analysis will examine a larger patient number, different automatic seizure detection parameters and programs, the utility of CSA, and yield of combining these methods.

1.097

AMBULATORY ELECTROENCEPHALOGRAPHY (EEG) IN ADULTS: DIAGNOSTIC YIELD AND TOLERABILITY

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Rationale: Inpatient video EEG telemetry monitoring is the gold standard to accurately diagnose epileptic versus non epileptic events and for the localization of epileptogenic areas in the assessment of patients for surgical treatment. This technique is expensive and requires specialized technical and human resource. Ambulatory EEG is a technique that allow to record EEG continuous activity when patients are at home without the necessity of admission to the hospital for prolonged video EEG monitoring

Methods: This is a prospective cohort study performed in a Canadian teaching center in order to assess the yield and tolerability of ambulatory electroencephalogram. In a period of three years forty nine patients were included. The yield was assessed taking into account the question performed before and after the investigation.

Results: Forty nine patients, aged 13-73 years, undergoing ambulatory electroencephalography (EEG) were prospectively recruited during a 36 months in Royal University Hospital, Saskatchewan. Our population consisted of fifteen males (30%) and thirty four females (70%).The age of onset of the events was 30.2 + 18.98 years with 7.42 + 10.36 years of evolution. Most of the patients had had previous routine EEG (98%) and 74% (37 EEGs) were normal. The most frequent reason (53% of the times) for ordered an ambulatory EEG was for the characterization of the spells (query non epileptic events), in 31% (15 patients) of the cases the ambulatory was order for the characterization of the spells with potential epileptic diagnosis. In 4 patients (8%) the ambulatory was order for work up in candidates for epilepsy surgery. Finally in 4% of patients (2) the indication of ambulatory was the characterization of the spells in patients with epilepsy (possible non epileptic events) and the quantification of spikes and seizures in two cases (4%). The minimum days with the ambulatory EEG was one day with a maximum of 3 days, the mean days of recording was 1.22 + 0.55 days. No complications were seen in the 49 included patients. The ambulatory EEG answered the clinical question in 70% (35) of cases. Of these, only in 22 (45%) of the patients was possible to recorded events, of these events 10 % (5) were seizures and the 90% were non epileptic. The most frequent reasons why the initial question was not answered were: the lack of recorded events (64 %) and the lack of epileptic activity in the recording (36%)

Conclusions: In this study, we found that ambulatory electroencephalography has a high diagnostic yield (70%), this is comparable with our Video-EEG rate (80%). We believed that a careful selection of patients is the most important factor to have a high diagnostic yield. The main utility of the ambulatory EEG is the characterization of patients with non epileptic events, in patients where the diagnosis of epilepsy is not clear and in the quantification of spikes and seizure to improve the medical management of patients. The ambulatory EEG is a cost effective solution for increasing necessities of Video-EEG

1.098

CONVERGENCE OF ICTAL HYPOXIA AND POSTICTAL HYPOVENTILATION AS A POTENTIAL MECHANISM OF SUDEP

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Rationale: Generalized tonic-clonic seizures (GTCS) are a major risk factor for sudden unexpected death in epilepsy (SUDEP). Postictal EEG suppression, arrhythmia, and hypoventilation are often observed in patients with GTCS. Nocturnal supervision seems to protect against SUDEP independent of seizure control. Here we characterize postictal EEG recovery, heart rate, and respiratory rate in relation to seizure management in patients with primary or secondarily GTCS. The findings may further delineate the role of ictal hypoxia and postictal hypoventilation in SUDEP.

Methods: We reviewed the medical records and video EEG of patients who underwent long-term monitoring at the University of Chicago medical center. We included 14 patients (4 men, 10 women) who had 1 to 2 GTCS. Mean age at evaluation was 39 years (20 to 78 years). Seizure duration ranged from 60 to 300 seconds. Five patients had primary GTCS and 9 patients had secondarily GTCS. We evaluated the EEG rhythm, heart rate, respiratory rate, and seizure management including oral suctioning and supplemental oxygen up to 2 minutes after seizure cessation.

Results: Thirteen of 14 patients (93%) demonstrated immediate postictal EEG suppression. Eleven of 14 patients (79%) had postictal tachycardia. Ten of 14 patients (71%) had postictal tachypnea. Twelve of the 13 patients (92%) with EEG suppression showed delta or theta slowing 5 to 80 seconds after receiving suctioning or supplemental oxygen. One patient had theta slowing regardless of seizure management. Two patients without seizure management had prolonged EEG suppression, tachycardia, and tachypnea. One of these 2 patients had an unwitnessed GTCS in prone position leading to SUDEP.

Conclusions: Postictal EEG suppression, tachycardia, and tachypnea are common features after GTCS. Postictal hypoventilation secondary to partial airway obstruction or pulmonary edema is postulated as one of the causes. Here we show that immediate seizure management facilitates the recovery of postictal EEG suppression, tachycardia, and tachypnea. Our findings suggest that the convergence of ictal hypoxia and postictal hypoventilation is a potential mechanism of SUDEP.

1.099

THE ROLE OF THE ELECTROCORTICOGRAPHY IN THE TAILORED TEMPORAL LOBE SURGERY DUE TO MESIAL TEMPORAL SCLEROSIS

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Rationale: Although intraoperative electrocorticography (ECoG) has been in clinical use for many decades, the validity of this procedure in guiding resective temporal lobe epilepsy is still uncertain. Currently, is considerate an important additional technique in the tailored temporal lobectomy, superfluous in standard anterior temporal lobectomy, and probably unnecessary in amygdalohippocampectomy. However, there are few papers published about the utility of ECoG in the tailored temporal lobectomy due to mesial temporal sclerosis. These studies have several methodological limitations, including the small number de patients, the missing residual epileptiform activity, the lack of homogeneous diagnosis and preoperative MRI studies.

Methods: We retrospectively included 20 patients who underwent tailored temporal epilepsy surgery guided by ECoG at our center from January 2007 through December 2010. We described the clinical characteristics, pathological, neuroimaging, interictal and ictal scalp video-EEG findings, nuclear medicine findings, ECoG abnormalities, anestethics protocols and outcome. We used descriptive statistical analysis.

Results: Twenty patients (6 men, 14 women) ranging from 23 to 47 years (mean 36.9 years) were analyzed. Seventeen (85%) patients showed interictal and ictal unilateral temporal onset, mainly right anterior temporal epileptic activity (52%). The ECoG recording showed pre-resection spikes both in mesial temporal lobe (MTL) and lateral temporal lobe (LTL) in 10 (50%) patients, restricted to the LTL in 7 (35%) and only restricted to MTL in 3 (15%) patients. Seventeen (85%) postsurgical ECoG recordings didn't show any remaining epileptiform activity, however, some residual epileptiform abnormalities were seen in 3 (15%) patients, two on the temporal posterior lateral surgical border and one on the third right frontal gyrus. Histopathological evaluation revealed hippocampal sclerosis in all the cases, except in one patient in which an additional cortical temporal dysplasia type IIB were found. Postsurgical follow-up range from 12 months to 2.5 years (mean, 16.3 months), following surgery, 15 (75%) patients were seizure free (IA), two (10%) patients only had auras (IB), two patients (10%) had rare seizures (1; IIA and 1; IIB) and only one patient had IIA outcome. Two patients developed vascular complications.

Conclusions: In our study 75% of our patients were seizure free, this outcome maybe is result of a non-standard and tailored neurosurgical approach. To our knowledge this is the first study in this selected population evaluated the role of the maximal residual resection of the epileptiform activity. However, more prospective and randomized studies with larger number of patients are required.

Clinical characteristics, neuroimaging findings, ECoG abnormalities and outcome of 20 patients that underwent tailored temporal lobe epilepsy due mesial temporal lobe epilepsy.

IMAGE: tables/907276_T1.jpg

R: Right, L: Left, F: Female, M: Male.. LTL:Lateral temporal lobe MTL: Mesial temporal lobe. HS: Hippocampal sclerosis

1.100

DIAGNOSTIC UTILITY OF CONTINUOUS EEG MONITORING AMONG CRITICALLY ILL CHILDREN

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Rationale: Continuous EEG monitoring (cEEG) permits the detection of convulsive and nonconvulsive seizures among critically ill children admitted to the intensive care unit (ICU). Several retrospective studies have reported high rates of nonconvulsive seizures among critically adults and children undergoing clinical cEEG monitoring.

Methods: Single-center retrospective review of clinical cEEG monitoring performed in our pediatric and neonatal ICUs between 2004 and 2009. We examined the indications for cEEG monitoring, the clinical characteristics of monitored patients, and the occurrence and timing of seizures.

Results: 258 cEEG studies were performed over a 70-month period on 194 patients, of which 24% were neonates. Seizures had occurred in 27% of patients prior to cEEG monitoring, and 31% had a prior diagnosis of epilepsy. Indications for cEEG monitoring were either therapeutic: to guide treatment of seizures or status epilepticus (47%); or diagnostic: to characterize clinical events suspected to be seizures (24%), to evaluate an unexplained alteration in consciousness (23%), and to monitor for seizures in paralyzed patients (5%). Duration of cEEG monitoring varied from 4 hours to 8 days, but was most commonly 12-24 hours. Seizures were detected in 50% of cEEG recordings, and in 50% of patients monitored. Nonconvulsive seizures occurred in 32% of patients. Nonconvulsive seizures were far more common among cEEGs performed for diagnostic purposes (89%), than among cEEGs performed for therapeutic purposes (26%). All seizures in the diagnostic cEEG group were captured within 24 hours of monitoring.

Conclusions: These findings confirm the diagnostic utility of continuous EEG monitoring among critically ill children. Nonconvulsive

seizures are more common among critically ill children monitored for diagnostic purposes than those monitored for therapeutic purposes. 24 hours of cEEG monitoring appears sufficient to detect seizures. The impact of cEEG monitoring on seizure treatment and outcomes requires further study.

1.101

CONTINUOUS VIDEO-EEG IN THE ICU

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Rationale: Prolonged EEG monitoring in the ICU is now common. Studies suggest that the prevalence of nonconvulsive status epilepticus (NCSE) is 10%. Isolated seizures may be more common. Despite this, the selection criteria for monitoring remain ambiguous, and the impact of prolonged EEG monitoring on treatment is unclear. We addressed these questions by doing prolonged EEG on patients for whom a routine or prolonged EEG was requested by ICU staff.

Methods: During a prospective but not randomized 22-month study, 130 ICU patients for whom staff requested an EEG were placed in 3 groups. One group received a 30-minute EEG. A second group, for whom staff requested a 30-minute EEG, instead got 16-24 hours of continuous video-EEG. The third group comprised patients for whom long-term video-EEG monitoring was requested to monitor suspected status epilepticus. Epileptologists compared the first 30 minutes of EEG with the subsequent recording to see if any additional information was obtained, and if it impacted treatment.

Results: 34 patients had a routine 30-minute EEG. 1 was normal, 27 were slow or poorly reactive, and 6 (18%) showed epileptiform activity, including one with electrographic seizures.

83 patients, who might have received only a 30 minute EEG, were monitored with video-EEG for 16-24 hours. These included patients with trauma (2), tumor (7), stroke (7), metabolic derangement (16), cerebral hemorrhage (22), and hypoxic-ischemic injury (29). All EEGs were abnormal with slowing and poor reactivity.

28/83 patients (34%) showed epileptiform findings in the first 30 minutes, including periodic epileptiform discharges (PEDs), generalized or focal epileptiform discharges, burst suppression, triphasic waves, and 2 patients with clinical seizures. 5/28 developed additional epileptiform changes overnight, including 2 with clinical seizures, and in 4 treatment was changed.

55/83 patients (66%) had no epileptiform findings in the first 30 minutes, but 7/55 developed these overnight, including 2 with electrographic and 1 with clinical seizures. In 3 patients treatment was changed. Overall, in 7/83 patients treatment was changed based on prolonged as opposed to routine EEG, and 3 showed improvement.

13 patients known to have epilepsy, who presented with seizures, were deliberately placed on long term video-EEG monitor. 9/13 (69%) showed epileptiform abnormalities in the first 30 minutes including 3 with NCSE and 1 with focal seizures. Overnight 2 more evolved into NCSE, and prolonged EEG influenced therapy in 6/13.

Conclusions: In 83 unselected ICU patients, overnight video-EEG, as opposed to a 30-minute EEG, detected additional epileptiform abnormalities in only 12 patients, and only 2 of those had clinically undetectable seizures. Only 7/83 patients (8%) had changes in treatment based on EEG findings. In contrast, patients with epilepsy who presented with seizures were more likely to have NCSE, and EEG guided treatment in 6/13 (46%). This study suggests that long-term EEG monitoring in an unselected ICU population has little benefit. In a selected population the benefit may be larger.

1.102

AUTOMATIC DETECTION OF INTRACRANIALLY RECORDED HIGH FREQUENCY OSCILLATIONS USING A RADIAL BASIS FUNCTION NEURAL NETWORK GIVES RELIABLE INFORMATION ABOUT THE DISTRIBUTION OF HFOS OVER ANATOMICAL REGIONS

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Rationale: High frequency oscillations (HFO) in the range between 80 and 500 Hz have been described to be recorded in seizure generating areas. The removal of HFO generating areas has been linked to a good postsurgical outcome. The visual identification of HFOs is a time consuming task and far from being unequivocal. Most automatic HFO detection algorithm described up to now use thresholds derived from global HFO feature statistics. Objective of the presented study was to replace these thresholds by the incorporation of human expertise in the detection algorithm using a radial basis function (RBF) neural network.

Methods: Basis of this study were intracranial grid and strip recordings with commercially available electrodes of 11 patients with pathologically confirmed focal cortical dyspalsia (FCD) suffering from epilepsy. This study was restricted to HFOs in the range between (80-200Hz), termed ripples. HFOs were visually marked in a three-minute segment of slow wave sleep using high-pass filters at 80Hz The input of the RBF neural network consisted of the normalized signal energy, normalized signal line length and normalized instantaneous frequency of the high-passed filtered signal. The instantaneous frequency was computed on the basis of the Hilbert Transformation. Visually marked HFOs of three patients were used to determine the parameters of the RBF neural network. The marked HFO events of the other 8 patients were used to evaluate the detection algorithm.

Results: In the segments of the 8 recordings used for evaluation 41722 HFOs were visually marked, whereas the RBF neural network detected 50606 HFOs. The percentage of overlapping detections was 30.7 %. Comparing the detections over channels the correlation of HFO count distributions over channels was significant between visual and automatic analysis for each of the data segments (min. correlation 0.366 ($p<0.05$), max. correlation 0.934 ($p<0.001$)). Rates of automatic detected HFOs were significantly higher inside the seizure onset zone SOZ (46.5/min) than outside (31.0/min, $p<0.001$).

Conclusions: Also the RBF neural network detector, which is able to include information from human expertise, achieved only a comparable low rate of about 30 % of detections matching with visual review. But there was a high concordance between electrode contacts and in conclusion anatomic regions, which show high HFO rates as well revealed by visual analysis as well as by the automatic detection as shown by the correlation of HFO counts and the HFO rates in relation to the SOZ. Thus, the RBF neural network HFO detector has the potential to reveal reliable information about anatomic regions with high HFO rates.

IMAGE: images/904635_A.jpg

1.103

DISCRIMINATION BETWEEN PREICTAL AND INTERICTAL PERIODS IN PATIENTS WITH TEMPORAL LOBE EPILEPSY USING CONTINUOUS WAVELET TRANSFORM IN HIGH FREQUENCY BANDS

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Rationale: Identification of consistent distinguishing features between preictal and interictal periods in the EEG is an essential step towards performing seizure prediction. Recent studies suggest that high frequencies (80-500Hz) in intracranial EEGs play a role in epileptogenesis and could potentially underlie seizure precursors. In this study, a continuous wavelet transform approach is proposed to derive discriminating features between the preictal and the interictal state in intracranial EEGs from patients with mesial temporal lobe epilepsy.

Methods: EEG signals (filtered at 500Hz and sampled at 2000Hz) from 6 randomly selected patients with mesial temporal lobe epilepsy, recorded from bilateral contacts in the hippocampus, amygdala and parahippocampus, were processed. 10 interictal segments of 1 hour and up to 6 preictal segments of 22 minutes were analyzed using a continuous wavelet transform in 4 frequency bands (50 to 450Hz). Wavelet entropy and energy were computed in the time-frequency domain for each segment. We defined a phase space of entropy and energy and hypothesized the existence of a reference state in this space defined in the 90s immediate preictal period. We characterized this reference state by a geometric region in this space. The parameters of this region were learned from training preictal datasets. We then compared the dynamics of the interictal and preictal distributions by computing their distance to the reference region and the inclusion rate, defined by the proportion of points in the phase space inside the reference region during a segment of 22 minutes.

Results: When computing the average distance to a reference state defined simply by the mean point of the immediate preictal distributions, 4 patients showed a consistent discrimination between preictal and interictal segments on at least one EEG channel and one frequency band (figure 1). Distances computed from interictal segments were consistently higher than those from preictal segments. Inclusion rates were higher in preictal periods on channels where discrimination was observed with average preictal/interictal rates of 73.5/18.6 for patient 1, 85.6/57.2 for patient 2, 68.2/1.6 for patient 3 and 93.4/20.4 for patient 4. We thus confirmed the existence of a reference state characterizing the immediate preictal period. Random samples of 90s taken from interictal and preictal segments produced distributions of mean points substantially different (at 5% confidence level) from actual immediate preictal values.

Conclusions: There exists a reference state behaving as an attractor in the immediate preictal period from which most seizures emanate. We proposed a discrimination technique between interictal and preictal periods based on the distance to this reference state. First results suggest that preictal periods are closer to the reference state than interictal periods in the entropy-energy phase space of a specific frequency band, opening the door to discriminating preictal from interictal periods.

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IMAGE: images/905681_A.jpg

Figure 1. Distances from moving windows (22 minutes large) of 5 interictal periods (color boxes) and preictal periods (red lines, 2 lines shown in patient 1, patient 3 and patient 4 illustrations overlap) to reference point for 4 patients. Preictals appear at closer average distance (dashed black lines) to reference state than interictals, suggesting discrimination in the defined entropy-energy phase space.

1.104

ABRUPT PHASE TRANSITION OF ICTAL ACTIVITY TEMPOROSPATIALLY

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Rationale: Not like anterior temporal lobectomy, extratemporal resective surgery would not provide sufficient control of neocortical seizures. Not only the ability to clearly define and completely resect the epileptogenic zone and the resectional limitation of eloquent regions, but also the unclear neurophysiology causes low average seizure-free rates of ~60% in extratemporal lobe epilepsy in comparison with over 90% seizure-free rate in mesial temporal lobe epilepsy. So in this study, we propose a method to show the seizure dynamics from burst frequency during a seizure that is more meaningful in neurophysiology and could be a useful tool to explore the seizure dynamics in clinical use.

Methods: The digitalized incranial EEGs were extracted from 14 patients with intractable extratemporal epilepsies. The focus/foci of epileptogeneis was/were identified by the seizure activities from the implanted subdural electrodes (with a mesial temporal depth electrode if mesial temporal lobe seizure could not be excluded). By Hilbert Huang Transform (HHT), the complex ictal ECoG signals were decomposed into different Intrinsic Mode Functions (IMFs). The 1st to 3rd components of IMF modes as main activity of epileptic neurons were chosen. Then the IMF modes were enveloped and taken. The neural burst frequencies were enhanced by using the autocorrelation function.

Results: The ictal stages over the seizure onset zone can be recognized and categorized into pre fast activity stage, fast spiking stage, phase transition stage, fast bursting stage and slow bursting stage. Over the region identified as seizure onset zone by visual assessment, a short train of high-frequency oscillation was unburied and the subsequent seizure stages were represented in the autocorrelogram remarkably. The adjacent recruited regions would also demonstrate similar periodic activity after seizure onset. No pre fast activity stage was found over the seizure propagated regions.

Conclusions: Based on the simple functions of HHT and autocorrelation, our method demonstrated the temporospatial seizure dynamics from the burst frequency at seizure onset to the subsequent seizure propagation that is more meaningful in ictogenic neurophysiology. The overview of each electrode corresponding autocorrelogram throughout the seizure activity supported the scenario that a focal seizure is caused by an abrupt transition. The change of stages following ictal onset is very sudden as well.

IMAGE: images/907318_A.jpg

IMAGE: images/907318_B.jpg

1.105

SOURCE LOCALIZATION OF EPILEPTIC FOCI FROM EEG

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Rationale: The main objective of this study was to develop a computational method for improving the localization of epileptic seizure foci in the brain based on multi channel EEG recordings. Unlike other EEG source localization methods such as LORETA, we were looking for a solution that specifically localize epileptic activity relative to the background of normal EEG activity and it does at a higher than electrode grid resolution.

Methods: Our basic assumption was that seizures manifest in EEG as large amplitude synchronized activity. We further assumed that this synchronized activity can be distinguished from the background EEG activity as zero phase lag (<2 ms) synchrony, as oppose to non-zero phase coherency, typical of traveling or spreading waves in the normal EEG. Therefore, we computed the point-to-point correlation of simultaneously sampled EEG signal between all 24 electrode pairs, placed according to the 10/20 system. The correlation-matrix contained all pair-wise correlation coefficients between the different channels. Theoretically, when the source of seizure is located in the cerebral cortex near the skull, it is detected as a localized synchrony between adjacent channels that is well distinguishable from other channels. In contrast, when the source is located in the deep structures the seizure may project to multiple electrode locations and manifest as synchrony between distant electrodes. In either case, we can identify those channels based on the magnitude of shared synchronized activity. The group of synchronized electrodes is identified as a cluster in the correlation-matrix. The next step was to interpolate between the synchronized channels to obtain a source location beyond electrode grid precision. By limiting the interpolation to the pre-selected channels the accuracy of the interpolation method improves significantly relative to other methods that take the activity over the entire skull into an account.

Results: We tested the algorithm on data obtained from two patients diagnosed with partial epilepsy. The EEG data consisted of identified epochs of seizure free EEG (wake state and sleep) and EEG during seizure activity, several minutes each. When the seizure-free recordings were compared with EEG records of seizures we found that the seizure prone areas are clearly distinguishable from non-seizure prone areas even during seizure-free activity based on synchrony. The localization provided by the correlation method was confirmed by MRI as well as by experts' judgments.

Conclusions: Based on the results from two patients under different conditions we concluded that the source localization of epileptic focus based on synchrony is not only feasible but may contribute to the practice of EEG diagnosis in two ways: (1) enables to localize the source at a higher than grid resolution and (2) it reveals the pathological region even during seizure-free EEG activity. The results suggest that it is worth to pursue this direction of research in order to develop more sensitive diagnostic methods for partial epilepsy.

IMAGE: images/843635_A.jpg

Localization during awake seizure-free state. (A) EEG segment (B) Whole EEG sample. (C) Correlation matrix. (D) localization map.

IMAGE: images/843635_B.jpg

Localization during seizure activity. (A) EEG segment (B) Whole EEG sample. (C) Correlation matrix. (D) localization map.

1.106

SPONTANEOUS AND VISUALLY-DRIVEN PHYSIOLOGICAL HIGH-FREQUENCY OSCILLATIONS MEASURED ON ELECTROCORTICOGRAPHY

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Rationale: High-frequency oscillations (HFOs) at 80 Hz and above can be observed on electrocorticography (ECoG) in humans. A widely-proposed hypothesis is that spontaneous HFOs during slow-wave sleep are likely to be epileptiform in patients with focal epilepsy, whereas HFOs driven by sensorimotor or cognitive tasks are physiological in nature. In this study, we determined the presence of physiological HFOs spontaneously emerging without external sensory stimuli.

Methods: We studied 10 patients with focal epilepsy undergoing extraoperative subdural ECoG recording. We determined whether HFOs are spontaneously generated by the non-epileptogenic occipital cortex during interictal slow-wave sleep. We then compared the spectral and spatial characteristics of such spontaneous occipital HFOs with those of HFOs driven by a visual task. We also explored whether the spectral frequency and amplitude of such spontaneous occipital HFOs differed from those of presumably epileptogenic HFOs emerging from the seizure focus outside of the occipital lobe.

Results: We identified spontaneous HFOs at g"80 Hz with a mean duration of 350 msec intermittently arising from the non-epileptogenic occipital lobe (Figure 1). The spectral frequency band of these spontaneous occipital HFOs was similar to that of visually-driven HFOs. Spontaneous occipital HFOs were spatially sparse and confined to smaller areas, whereas visually-driven HFOs involved larger occipital areas and were propagated to the rostral direction more extensively. Neither spectral frequency band nor amplitude of spontaneous occipital HFOs of physiological nature were significantly different from those of epileptogenic HFOs arising from non-occipital seizure focus. Spontaneous occipital and epileptogenic HFOs differed in the way their occurrence was coupled to the phases of delta-oscillations. Epileptogenic HFOs were approximately equally and strongly locked to the phase of delta activity in the range from 1.0 to 3.0 Hz. As opposed to that, for spontaneous occipital HFOs, the strength of delta-phase coupling decayed from 1.0 to 3.0 Hz (Figure 2).

Conclusions: HFOs of physiological nature are spontaneously generated by the occipital cortex during slow-wave sleep; this observation should be taken into consideration when epileptogenic HFOs are utilized to determine the extent of cortical resection in the context of epilepsy surgery. Coupling of spontaneous delta and HFOs may increase the understanding of the significance of delta-oscillations during slow-wave sleep.

This study was supported by NIH grants: NS47550 & NS64033 (to E. Asano).

IMAGE: images/896530_A.jpg

Figure1: The extent of high-frequency oscillations (HFOs) and delta-oscillations in patient #5. (A) The locations of subdural electrodes are shown. Channels 1, 2, and 3 were located in the occipital pole. Channel

2 was defined as the occipital site of interest. Channel 4 was located in the ventral occipital-temporal area. Channels 5 and 6 were located in the lateral temporal area. Channel 6 was defined as the epileptogenic site of interest. (B) Left column: Spontaneous occipital HFOs were confined to the occipital pole; no significant HFOs were observed at channel 4 in the ventral occipital-temporal area. Middle column: Epileptogenic HFOs were confined to the lateral temporal area. Right column: Following the onset of visual stimuli, visually-driven HFOs arose from the occipital pole and were propagated to Channel 4 in the ventral occipital-temporal area. Following the offset of visual stimuli, visually-driven HFOs in the occipital pole gradually subsided.

IMAGE: images/896530_B.jpg

Figure2: Delta phase distributions. Shown are the distributions of delta-phases in patient #5 at the peak of spontaneous occipital HFOs and the peak of epileptogenic HFOs.

1.107

A COMPARISON OF AUTOMATIC DETECTORS OF HIGH FREQUENCY OSCILLATIONS

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Rationale: High Frequency Oscillations (HFOs) are emerging as a biomarker of epileptogenic tissue. Visual marking of HFOs can be performed, but it is highly time consuming and subjectivity is inevitable. Thus, the development of automatic HFO detectors is crucial for the systematic study of HFOs and for their eventual utilization in clinical settings. At present, only a handful automatic detectors exist. In this study, a systematic comparison of the detectors on the same data set is presented.

Methods: Intracerebral EEGs from 20 randomly selected patients were processed (filtered at 500Hz and sampled at 2000Hz). HFO events were identified independently by two experienced reviewers in all functioning channels during one minute of slow wave sleep. In addition, baseline segments (where it was clear that no oscillation was present) were visually marked. Channels with nearly continuous high frequency activity were excluded, resulting in 278 channels. These channels included 5238 visually identified HFO events (positive events) and 51076 visually identified baselines (negative events) that were used as the gold standard events. Four automatic HFO detectors were compared. Three are based on the comparison of the energy of the signal with the EEG epoch that includes the events. The main difference among them is the type of energy function computed on the filtered signal, either the root mean square amplitude (Staba et al., J Neurophysiol 2002; 88: 1743-52), the short-time line length (Gardner et al., Clin Neurophysiol 2007; 118: 1134-43), or the Hilbert envelope (Crépon et al., Brain 2010; 133: 33-45). The fourth detector, the MNI detector (Zelmann et al., IEEE EMBS 2010, submitted), first detects baseline segments, where no oscillatory activity is present, and then compares the energy (root mean square amplitude) of the EEG signal with that of the detected baselines. In this way, the local characteristics of the background are considered. Receiver Operator Curves (ROC) were computed for each channel and averaged. The threshold values were computed according to the specifications of each detector.

Results: The MNI detector had significantly higher sensitivity than the others, but at a cost of significantly higher false positive rate (FPR). Figure 1 presents the average ROC and performance table. The overall low FPR is not surprising, since we are only considering as reference negative events those segments of EEG visually marked as baselines. Thus, not all the EEG signal was considered in this study. The main difference in performance is observed in very active channels. Figure 2 shows an example of such channels, where one HFO is detected by all detectors whereas another is detected only by the MNI detector.

Conclusions: Each automatic detector was developed for different EEG recordings and with different aims. Given the lack of a formal definition of HFOs, comparing them in a single data set is important to analyse their performance. The MNI detector performed better than the others in this dataset, but has larger FPR and was developed on channels similar to those used for testing.

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IMAGE: images/899184_A.jpg

Figure 1. ROC comparing the performance of all detectors. Table with mean sensitivity and flase positive rate (FPR) for each detector's operating point. The MNI detector has a much better sensitivity, but worse FPR. Markers represent different threshold levels. Note non-standard ROC scale. Filters were modified to 80-450Hz. *GarnerDetector: equalization filter was removed.

IMAGE: images/899184_B.jpg

Figure 2. Examples of HFOs detected in a very active channel. A) HFO detected by all detectors. B) HFO detected only by the MNI Detector. This detection and the reference (visual) marking are indicated. Top: unfiltered EEG. Bottom: filtered (80-450Hz) signal. Note 5 times difference in scale.

1.108

ELECTROCORTICOGRAPHIC CORRELATES OF COGNITIVE CONTROL IN A STROOP TASK -INTRACRANIAL RECORDING IN EPILEPTIC PATIENTS-

Eishi Asano, S. Koga, R. Rothermel, C. Juhasz, T. Nagasawa and S. Sood (Children's Hospital of Michigan, Detroit)

Rationale: The human brain executes cognitive control, such as selection of relevant information in the presence of competing irrelevant information, and cognitive control is essential for us to yield a series of optimal behaviors in our daily life. The present study assessed electrocorticographic gamma-oscillations elicited by cognitive control in the context of the Stroop color-naming paradigm, with a temporal resolution of 10 msec and spatial resolution of 1 cm.

Methods: We studied a consecutive series of five native English-speaking patients with a diagnosis of medically-uncontrolled focal seizures (age range: 10 - 17 years; three females), who underwent extraoperative electrocorticography recording. Subjects were instructed to overtly read a color word printed in an incongruent color in the reading task (e.g.: to answer 'Red' when a word 'Red' printed in blue ink was presented), and to overtly name the ink color of a color word printed in an incongruent color in the Stroop color-naming task (e.g.: to answer 'Blue' when a word 'Red' printed in blue ink was presented).

Results: The Stroop color-naming task specifically elicited larger gamma-augmentations in the dorsolateral-premotor, dorsolateral-prefrontal and supplementary motor areas with considerable inter-subject spatial variability. Such Stroop color-naming-specific gamma-augmentations occurred approximately 500 to 200 msec prior to overt responses. Electrical stimulation of the sites showing Stroop color-

naming-specific gamma-augmentations resulted in temporary naming impairment more frequently than that of the remaining sites.

Conclusions: This study has provided direct evidence that a critical process of cognitive control in the context of Stroop color-naming paradigm consists of recruitment of neurons essential for naming located in variable portions of the dorsolateral premotor and prefrontal areas.

1.109

AUTOMATIC SEIZURE DETECTION IN SEEG USING HIGH FREQUENCY ACTIVITIES IN WAVELET DOMAIN

Leila Ayoubian and J. Gotman (Montreal Neurological Institute, McGill University, Montreal, QC, Canada)

Rationale: Automatic seizure detection is often used during long-term monitoring. Existing automatic detection techniques show high sensitivity and moderate specificity, and detect seizures relatively long time after onset. Analysis of high frequency activities (HFs), ranging from 80-500 Hz, indicates that these activities are prominent in many seizures and occur at seizure onset (Jirsch et al 2006, Ochi et al 2007).

This study explores the use of HFs for automatic seizure detection in SEEG, as they have not been used before and may enhance the performance of existing methods.

Methods: The SEEG was recorded after 500 Hz filtering with 2000 Hz sampling rate. The method was designed using 2 h of SEEG from 8 patients and a total of 10 seizures.

SEEG signals were transformed into wavelet domain using the complex Morlet wavelet. The frequency ranges of interest are between 80-500 Hz. This method employed wavelet analysis of sequential 5s epochs in a sliding window to avoid edge effects. The algorithm was designed to extract features from each epoch and compare them with the features from a constantly updated background lasting 100 s and located 20 s before the current epoch. The method is aimed at detecting two features for each of 15 frequency bands with 30 Hz resolution between 80-500 Hz. The features are the number of HF discharges and the entropy. Features with values greater than 3 and 5 standard deviations above the mean were thresholded. Combinations of thresholded features were then used to mark significant HFs for detection.

Results: HFs are very prominent at seizure onset. The method was evaluated on data from 8 patients and its performance was measured based on sensitivity, false detection rate and delay between seizure onset and detection. Results for the two threshold values, 3 and 5, show sensitivity of 100% and 70%, false detection rate of 0.68/h and 0.06/h and median delay of 6.1 s and 15 s, respectively. Examples are shown on figures 1 and 2. Missed seizures are characterized mainly by minimal or absent HF. False detections are mainly caused by short burst of spikes or harmonics of alternating current (60-Hz) artifact. For threshold value 3, excluding false detections caused by 60Hz, which could easily be identified, the false detection rate would become 0.43/h.

Conclusions: We have demonstrated that in SEEG it is possible to detect many seizures automatically through HFs only. As some seizures show minimal amounts of this activity, HFs are not sufficient to detect all seizures. However HF detection could be combined to existing seizure detection methods due to the fact that HFs are prominent early in the discharge and are relatively specific to seizures; this would thus improve seizure detection performance.

Grant support: Work supported by CIHR grant # MOP-10189

References:

Jirsch et al.,(2006) Brain 129: 1593-1608

Ochi et al.,(2007) Epilepsia 48 , pp. 286-296

IMAGE: images/905786_A.jpg

(A) Wavelet transform representation for channel LH1-LH2. The power of the oscillation is depicted by a color scale code. The appearance of HFs at seizure onset, with dominant frequency components at approximately 80-200 Hz and 250-400 Hz is clearly visualized by high magnitude shown in white rectangles. The increase of HFs lasts into the seizure more intensely as spiking activities later predominate. (B) Fifteen seconds of raw SEEG recordings for 3 channels with the channel labels on the left.

IMAGE: images/905786_B.jpg

(A) Wavelet transform representation for channel LO2-LO3. The power of the oscillation is depicted by a color scale code. The absence of HFs during the ictal state indicates HFs are not sufficient to detect all seizures. (B) Fifteen seconds of raw SEEG recordings for 3 channels with the channel labels on the left.

1.110

INTRACRANIAL INTERICTAL SPIKE DETECTION: USE OF A NOVEL WAVELET BASED DETECTION SCHEME

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Rationale: In large part, the focus of the epilepsy community has been to develop approaches to control or eliminate seizures. Recently, in addition to the seizure events themselves, attention has been devoted to interictal spike events (IISEs) prevalent in a large fraction of patients. These IISEs appear as high frequency, high amplitude electrophysiological signals in scalp or intracranial field potential recordings (IFPs). The overarching goal of our work is to further our understanding of the effects of intracranial IISEs through their potential role in the disruption of cognitive function, by combining neurophysiological recordings in the human brain, psychophysical measurements, and computational data analyses. We present here the first phase of our goal, namely the detection of these IISEs, with the view to instituting our algorithm in an automated detection system.

Methods: Human scoring of epileptiform artifacts in scalp recordings or in IFPs is time consuming, and performance tends to decline when annotations are performed over long periods of time. We have developed an IFP IISE detection algorithm that uses wavelet analysis as a means for detection. Our algorithm is trained and tested on (separate) data sets of IISEs as delineated by clinicians. The algorithm convolves the IFP with a pattern adapted wavelet which matches the IISEs defined in our training set. We threshold over normalized wavelet coefficients to determine the detections (1).

Results: The intracranial IISE detection algorithm has been validated against IISEs as determined by agreement among a majority of (four) clinicians. Figure 1 demonstrates the mean IISE as marked by one clinician in a single electrode in right medial temporal lobe (electrode 11)

over the course of one hour of invasive intracranial monitoring. Figure 2 demonstrates performance curves for the algorithm. The training set of the algorithm consisted of half an hour of IFP, with the testing set consisting of the following half hour. The curves in Figure 2 show how the sensitivity of the algorithm scales with the number of false positives per minute, where the algorithm's performance is validated against spike times as determined by the overlap of at least three (out of four total) clinicians (red), or all four clinicians (black). In the latter case, over the half hour of testing (6 clinician determined IISEs total), we achieve a sensitivity of 100% at the cost of ~ 0.43 false positives per minute (~13 false positives total).

Conclusions: This pattern adapted wavelet based algorithm has now been tested on a database of recordings. The algorithm will be used in a real-time fashion to gate the presentation of an inventory of images by the occurrence of IISEs - we subsequently aim to measure the potential clinical effects of IISEs on patients with epilepsy during a variety of memory and cognitive tasks, and in a variety of cortical locations.

1. Latka M, et al., Wavelet analysis of epileptic spikes. Phys. Rev. E. 67, 052902 (2003).

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IMAGE: images/904926_A.jpg

Figure 1. Mean IISE as computed from the annotations of one clinician over one hour of IFP recording from a single electrode (electrode number 11) in right medial temporal lobe (RMT). Error bars represent one standard error of the mean. The mean IISE is shown in three different representations. "CA" refers to the common average signal (where the average includes electrode 11) from the strip placed over RMT.

IMAGE: images/904926_B.jpg

Figure 2. Performance curves obtained by validating the algorithm against a database of clinician determined IISEs, where the IISE times were computed from the overlap between at least three (out of four total) clinicians (red), and all four clinicians (black). The algorithm is trained on the first half hour of one hour of IFP recording and is tested on the second half hour. TP = true positives, FN = false negatives, FP = false positives. The total number of true positives in the testing set is: 19 IISEs (red), and 6 IISEs (black).

1.111

EEG SOURCE LOCALIZATION IN MALIGNANT ROLANDIC-SYLVIAN EPILEPSY

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Rationale: Malignant rolandic-sylvian epilepsy (MRSE)in children has been defined as a form of epilepsy characterized by medically refractory sensorimotor seizures, normal MRI, frontocentral EEG spikes, and cognitive problems. Rolandic-sylvian spike sources have previously been identified. We present 3 patients with MRSE who underwent EEG source analysis to further localize their epileptogenic zones.

Methods: Three children with MRSE ages 3-4 years underwent EEG source localization using BESA software. Scalp EEG was recorded using 10-20 international system with placement of additional electrodes at F9/F10 and P9/P10 for more accurate source localization. EEG activity was digitally recorded referentially to midline electrodes. Continuous monitoring with digital video and EEG was performed using the Nicolet digital video/EEG system. Dipole source analysis was done on routine scalp EEG using BESA software. All three children had interictal epileptiform discharges, as well as averaged waveforms, analyzed. Two children also had ictal discharges analyzed. Principle Component Analysis was used to separate potential concurrent sources. In the one child who had surgery thus far, the BESA analysis was done retrospectively on non-invasive scalp EEG.

Results: All 3 children had similar seizure semiology consisting of repetitive eye-blinking, head nodding, and oro-lingual automatisms. EEG dipole analysis for all 3 children showed localization in the lower peri-rolandic region. Individual and averaged waveforms both showed a source in this region. During cortical stimulation in the surgical patient, stimulating the area under the ictal-onset zone elicited rapid eye blinking similar to the seizure semiology. This was the cortical region subsequently resected. That child is currently seizure free.

Conclusions: BESA localized a very consistent epileptogenic region in all three children, who also all had very similar seizure semiology. In the one child that has required epilepsy surgery, the BESA retrospectively predicted a source that was very close to the resected cortical region. In future studies, it may be beneficial to study and compare dipole sources of both benign rolandic epilepsy and malignant rolandic-sylvian epilepsy to see if discernable features exist that may differentiate the two syndromes.

1.112

VARIABILITY OF NAMING-RELATED FUNCTION AS OBSERVED WITH EVENT-RELATED ELECTROCORTICOGRAPHY

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Rationale: Cortical mapping of language-related naming function is an important component of the presurgical evaluation of patients with medically intractable focal epilepsy. Previous studies reported probability maps generated using either electrical brain stimulation (EBS) or functional magnetic resonance imaging (fMRI). However, there are reports that find EBS inadequate for language mapping in children younger than 10 years of age (Schevon et al., Epilepsia, 2007) and fMRI an unsuitable replacement at present (Giussani et al., Neurosurgery, 2010). A more recently developed approach of mapping language cortex involves detection of gamma-augmentation that represents cortical activation driven by a task. In the present study, we have generated naming probability maps using event-related gamma-augmentation on electrocorticography (ECoG) and determined the inter-individual variability in localization of cortices involved in auditory language functions.

Methods: We studied 10 patients with focal epilepsy who underwent extraoperative ECoG and subsequent resective epilepsy surgery. All patients underwent preoperative MRI and an auditory naming task for cortical mapping using EBS as well as ECoG. They completed up to 100 question-and-answer trials recorded and integrated with ECoG.

Questions were designed to elicit 1 or 2 word answers; e.g. Q: 'What flies in the sky?' ECoG traces were temporally locked to response-onset and transformed into time-frequency matrices. To create an average probability map of naming function, all ECoG electrode positions in native space were transferred into MNI152 template space using landmark-constrained conformal cortical mapping (Muzik et al., Int J Biomed Imaging, 2007).

Results: The question-and-answer task required up to 20 minutes of each patient's time. Our findings indicate gamma-augmentations sequentially involving bilateral posterior superior temporal gyri, posterior left middle and inferior frontal gyri, and bilateral inferior pre- and post-central gyri. Gamma-augmentations in the superior temporal gyri driven by auditory stimuli as well as those in the pre- and post-central gyri driven by vocal responses were highly consistent across individuals in localization. However, gamma-augmentation during a delay period between auditory stimulus and vocal response had highly variable inter-individual localization and involved variable portions of the left frontal and temporal areas.

Conclusions: Naming-related gamma-augmentations may identify cortex participating in naming activity in both hemispheres. This time-efficient technique may reveal how cerebral cortex participates in auditory-naming processing in patients with focal epilepsy. We have found that gamma-augmentations during the delay period are highly variable in cortical localization among patients. These preliminary data are consistent with our working hypothesis that ECoG data can be used to generate a probability map of naming in humans.

1.113

INDEPENDENT COMPONENT ANALYSIS OF EEG REVEALS THE CEREBRAL GENERATORS AND PROPAGATION PATHWAY OF MYOCLONUS

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Rationale: This study uses independent component analysis (ICA) to investigate the dynamic interactions of independent dipoles in the EEG of myoclonus. Using ICA and dipole fitting algorithm, the mixed dynamic signals of scalp recorded electroencephalography (EEG) could be statistically separated into independent dipoles, which are presumed to be the cerebral generators of the recorded EEG. The complex dynamics between the independent dipoles in myoclonus could be characterized to reveal the cerebral generators and propagation pathways.

Methods: Retrospective EEG recordings from patients (n=7) with persistent myoclonus were selected according to the approved protocol by the institutional review boards. These EEGs were processed in EEGLAB (http://www.sccn.ucsd.edu/eeglab/). After computing ICA, the components of interest in generating myoclonus were identified using statistical analysis, autocorrelation. New EEGs were reconstructed and compared to the original EEGs to visually review the adequacy of component selection. Dipole fitting of these components was performed and mapped on a 2-d head model. The dynamic interactions of these components were reviewed on a video clip to review the probable propagation pathways for myoclonus.

Results: In 7 subjects with myoclonus, which was confirmed by clinical inspection and video recordings during the EEG recording, the locations of the cerebral generators were identified. Most of the fitted dipoles were dispersed within the mesial frontal lobe regions and the upper brainstem, with some scattering in the occipital/temporal lobes. The interactions and dynamic relationship of the anteriorly and posteriorly located dipoles were further analyzed. It was noted that there is a general pattern of front to back propagation of the dipole activity during myoclonus.

Conclusions: 1) A cerebral network involving the cerebral generators in the mesial frontal region and upper brainstem are implicated in generating myoclonus.

2) The mesial frontal region might be involved in the initiation of the myoclonus, with subsequent propagation of the activity to the upper brain stem.

1.114

PHASE COUPLING AND NETWORK PROPERTIES ARE ABNORMAL IN IDIOPATHIC GENERALISED EPILEPSY PATIENTS AND THEIR RELATIVES

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Rationale: Idiopathic generalised epilepsies have a complex inheritance pattern and are predominantly polygenic (Epilepsia 2005;46(S10):7-14). Previous studies support the genetic basis of both qualitative non-epileptiform and epileptiform EEG traits, with an increased prevalence of epileptiform abnormalities in unaffected relatives of patients with epilepsy compared with controls (Acta Neurol Scand. 1996;93(1):9-13). These characteristic abnormalities or 'endophenotypes' in clinically unaffected relatives may represent a genetic liability to develop symptoms. Characterising such traits could be of considerable use both for understanding seizure pathology, and for identifying individuals at increased risk. Given that epilepsy is characterised by abnormalities in the synchronisation of neuronal activity (Neuron 2006; 52(1):155-68), we sought to identify altered synchronisation properties and network topology in a group of patients with idiopathic generalised epilepsy and their first degree relatives using quantitative methods.

Methods: We recorded resting, eyes-closed EEG data from 15 patients with idiopathic generalised epilepsy (IGE), 19 of their unaffected relatives, and 24 healthy controls. The phase locking factor (PLF) was calculated for each pair of channels in several different frequency bands, and compared between groups. Additionally we transformed this phase locking data into a series of unweighted graphs, and assessed, for each network, basic facets of network topology including the clustering coefficient and path distance. We then compared these network properties between groups.

Results: IGE patients differed significantly from controls in mean PLF ($p=0.025$, averaging across all frequency bands) and mean clustering coefficient ($p=0.33$) with a strong trend towards significance for mean path length ($p=0.073$). In each case clinically unaffected relatives showed a similar pattern of difference from controls. This was significant in the case of mean clustering coefficient ($p=0.047$) and showed a strong trend towards significance in the case of of mean PLF ($p = 0.063$, averaging across all frequency bands). These differences were more pronounced at higher frequencies.

Conclusions: Our data strongly suggests that IGE is associated with significant changes to the phase synchronisation properties and network topology of resting electrical activity. They also provide evidence that such changes are found in clinically unaffected relatives of

patients with IGE, suggesting that such abnormalities may by characteristic of those with a high liability to develop IGE.

1.115

ROBUSTNESS OF NONLINEAR DYNAMICAL MEASURES OF EEG IN THE TIME-FREQUENCY DOMAIN: APPLICATION TO SEIZURE PREDICTION

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Rationale: One of the most debilitating aspects of epilepsy is the seemingly unpredictable occurrence of seizures (ictal states). The ability to predict epileptic seizures well prior to their occurrences may lead to the treatment of epilepsy along the lines of neuromodulation, that is, via timely electromagnetic stimulation and /or administration of anti-epileptic drugs, tens of minutes prior to a seizure onset (preictal period), to disrupt the observed entrainment of the dynamics of normal brain sites with the epileptogenic focus. In the past, Iasemidis et al. first reported results from testing a prospective seizure prediction algorithm using the nonlinear measure of short-term maximum Lyapunov exponent to measure the stability of the EEG in the time domain. Herein, we introduce a novel approach to detect preictal transitions in brain dynamics, and hence further assist seizure prediction, that measures the stability of the EEG in the time-frequency domain.

Methods: Intracranial long-term EEG recordings from five patients with temporal lobe epilepsy (TLE) were analyzed. First, a time-frequency transform was generated per electrode site and EEG segment. Second, a state space was created from the time-frequency transform of each EEG segment and the measure of the respective brain site’s stability of dynamics was estimated in that state space. Thus, the stability of the dynamics of the spectral probability distribution of the brain’s electrical activity per EEG segment and electrode site is captured. Next, the spatio-temporal synchronization between the stability measures at critical cortical sites over time was quantified using a student’s t-test. The predictability of each seizure was then estimated as the period before a seizure’s onset during which synchronization between critical sites is highly statistically significant (á=0.01). The mean predictability time across seizures from this new method was estimated and then compared to a frequency-domain-only-based approach for reconstruction of the state space.

Results: For the vast majority of the recorded seizures (>90%), the new algorithm detected preictal periods and estimated long predictability periods in the order of tens of minutes. The corresponding preictal entrainment of dynamics profiles of the involved critical brain sites were similar to the ones reported in the past from the time domain, using the method of delays per electrode for state space reconstruction, with a more abrupt and discernible postictal disentrainment. Finally, the measure of time-frequency stability introduced herein resulted to longer predictability times than the ones from a frequency-domain-only-based approach.

Conclusions: The seizure predictability and prediction results from the new algorithm imply the robustness of the existing algorithms for seizure prediction with respect to the parameters involved in the creation of the state space they work on. In addition, the new methodology may contribute to further improvement of the sensitivity and specificity of existing seizure prediction algorithms.

1.116

COMPUTER-ASSISTED IDENTIFICATION AND QUANTIFICATION OF STEREO-EEG FREQUENCY DURING ICTAL EVENTS, CLINICAL AND PHYSIOLOGICAL CORRELATES OF THE IDENTIFIED PATTERNS

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Rationale: Approximately half of the patients with a diagnosis of pharmaco-resistant epilepsy are potential candidates for epilepsy surgery. In 30-40% of drug-resistant patients with focal epilepsy the cerebral areas responsible for seizure generation can only be defined by intracranial recordings. The correct pre-surgical identification of the epileptogenic zone with intracranial recordings has a direct impact on post-surgical outcome. At present, the identification of the epileptic zone is based on visual inspection of the intracranial EEG. One of the principal impediments to computer-driven analysis of intracranial signals is the complexity and the quantity of data recorded during pre-surgical stereo-EEG sessions.

Methods: A new method for stereo EEG analysis was developed to retrospectively evaluate pre-surgical intracranial recordings in patients with pharmaco-resistant partial epilepsy. StereoEEG data were exported to a program developed in LabView for elaboration. Prevalent frequencies during seizure events were evaluated by Fourier transformation and further integral algorithms. Different frequencies and the relative powers were simultaneously evaluated in all recording leads. Patterns characterized by specific and prevalent frequencies were identified in a subset of recording sites during both seizure onset and seizure development. 3D-maps of the measurements obtained from each recording channels were reconstructed on magnetic resonance coordinates to visualize the spatial distribution of the analyzed contacts.

Results: Fast activity at 20-40 Hz was typically observed at the onset of seizures and during interictal period. During seizures a faster activity (50-250 Hz) of lower voltage, coupled with a very slow wave deflection was observed. The clinical correlates of these patterns were also analyzed. Seizure termination was characterized by a recovery of fast activity at 20-40 Hz that in most cases evolved into high amplitude bursts separated by brief EEG flattenings.

Conclusions: The present report describes a new computer-assisted method developed to analyze intracranial EEG traces. With this method, the reproducibility of ictal patterns in the same patient was characterized and the spatial distribution of specific StereoEEG signals associated with different types of seizures was recognized. In addition to the obvious clinical and diagnostic implications, the use of quantified analysis of intracranial EEG signals recorded directly into seizure generators could contribute to understand the neurobiological mechanisms responsible for the initiation and the propagation of focal seizures in humans.

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1.117

INTERICTAL EEG DYNAMICS IN PATIENTS WITH NON-EPILEPTIC SEIZURES VERSUS THOSE WITH TEMPORAL LOBE EPILEPSY

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Rationale: Similarities in the clinical manifestations of non-epileptic seizures (NES) and epileptic seizures (ES) can lead to erroneous diagnosis and treatment. Examination of EEG recordings from these patients can greatly enhance the likelihood of correctly identifying patients with ES. However, this diagnosis cannot be made conclusively without the presence of interictal or ictal epileptiform discharges, which may not be recorded during routine EEGs. As a result, multi-day EEG monitoring may be required to establish the diagnosis. Therefore, it would be beneficial to develop a diagnostic method that can reliably distinguish the EEG patterns of NES patients from those of patients with ES by analysis of brief interictal epochs of EEG. We investigated the existence of differences in signal characteristic dynamics of interictal EEGs recorded from NES and ES patients.

Methods: Interictal EEG epochs (at least 10 seconds each) were sampled from long-term EMU recordings obtained from 14 patients - seven were diagnosed as ES patients with TLE and the remaining seven as NES patients. To reduce confounding effects due to variability during the interictal period, sampling of the interictal EEG epochs were constrained with the following three conditions: 1) no epileptic discharges; 2) no eye-blinking; and 3) clear alpha rhythmic activities in the occipital region. Therefore, all sampled EEG epochs were recorded during an eyes-closed and relaxed state without the presence of epileptic discharges. A total of 139 and 211 epochs were sampled from ES and NES patient groups, respectively. The mean signal regularity (using the pattern-match regularity statistic, PMRS) and inter-hemisphere signal correlation (using maximal cross-correlation, CCmax) over the temporal lobe region (i.e., F7, F8, T3, T4, T5, and T6) were calculated for each EEG epoch. Nested one-way ANOVA was applied to test the hypothesis that there exists a significant ($p < 0.05$) difference between the two patient groups with respect to these two signal characteristics of EEG dynamics.

Results: The mean PMRS over ES patients was 0.461 (s.e. = 0.015) and was 0.496 (s.e. = 0.013) across NES patients (p-value = 0.018). The mean CCmax of ES patients was 0.283 (s.e. = 0.011) and was 0.333 (s.e. = 0.008) for NES patients (p-value = 0.007).

Conclusions: These results suggest that EEG signals over temporal regions in ES patients are more regular but are less correlated between the two hemispheres. If these results hold in a large-sample study, it may be possible to develop a diagnostic tool that can enhance the usefulness of routine EEG recordings in the diagnosis of epilepsy.

1.118

SPATIOTEMPORAL DYNAMICS OF STOCHASTIC BEHAVIOR OF PHASE SYNCHRONIZATION: LOCALIZING EPILEPTIC ZONES WITH INTERICTAL EEG

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Rationale: We examined the spatiotemporal dynamics of stochastic behavior of phase synchronization from interictal 256-channel scalp EEG recordings in patients with proven epilepsy to determine if these measures are useful in localizing epileptogenic zones.

Methods: We studied four patients with refractory epilepsy who underwent intracranial EEG to establish the localization of seizures. Prior to invasive EEG studies the subjects underwent dense array 256 channel EEG (dEEG) recordings. One minute of interictal dEEG was selected for analysis. The selected segment was at least two hours from an electrographic seizure and, based on visual analysis, free of interictal epileptiform patterns. Excessively noisy channels were removed and replaced with averages of surrounding electrodes. Data were imported into MATLAB for analysis. The EEG data was filtered in the theta (3-7 Hz), alpha (7-12 Hz), beta (12-30 Hz) and low gamma (30-50 Hz) band. The phase synchronization index (SI) was computed after taking Hilbert transform of the EEG data. The SI between a pair of channel was inferred from a statistical tendency to maintain a nearly constant phase difference over a given period of time even though the analytic phase of each channel may change markedly during that time frame. The SI for each electrode was averaged over with the nearby six electrodes. A detrended fluctuation analysis (DFA) was used to find the stochastic behavior of the SI. Contour plots with 5.0 sec intervals were constructed using a montage of the layout of 256 electrode positions.

Results: Contour plots displayed over the scalp show that the stochastic behavior of the SI becomes stronger with time in the proven epileptogenic area while in other areas it becomes fragmented and scattered. For two subjects, we were able to identify the epileptogenic area after examining the stochastic behavior for 30 sec. For the third subject it required 45 sec and for the fourth subject, 60 sec to localize the epileptogenic area. Dynamic stochastic behavior was best demonstrated in the low gamma and beta bands, in relation to the epileptic sites. On the other hand, the theta band activity was depressed for all four subjects in the epileptogenic area. The alpha band activity did not show any distinguishable spatiotemporal patterns in regard to the epileptogenic zones.

Conclusions: Examination of 60 sec of stochastic behavior of phase synchronization, derived from interictal scalp dEEG that is free of epileptiform discharges, has the potential to assist in localizing epileptic sites in subjects with proven epilepsy.

1.119

COMPARATIVE STUDY OF COMPLEXITY AND ENTROPY DURING ONSET OF PARTIAL EPILEPTIC SEIZURES

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Rationale: Several methods assessing the complexity and entropy of biological signals can be used to investigate properties of the EEG during onset of partial seizures (PS). The relative efficiency of these methods is reported here.

Methods: A subset of the most common methods assessing signal properties were selected for comparison. These include Shannon entropy (ShEn), spectral entropy (SpEn), sample entropy (SampEn), permutation entropy (PermH), Hjorth complexity, Lamberti complexity (CJS), LZC algorithmic complexity (Lempel-Ziv), signal complexity (GAD) and Higuchi fractal dimension (HFD). Each method was tested over a large set of partial seizures, both mesial temporal (MT), neocortical temporal (NeoT) and extra-temporal (NeoXT) onset, recorded from 45 consecutive patients with intracranial arrays. Normalized changes relative to an interictal baseline level were

calculated for preictal periods and for ictal periods IC1 (0-8s) and IC2 (6-14s) after onset.

Results: Changes observed during IC1 and IC2 periods are described here. Hjorth complexity shows a decrease for the MT group. LZC shows increases for all regions, the largest being for the NeoT group. GAD complexity exhibits early and fairly consistent increases for all regions. ShEn and SpEn are indicators of amplitude and frequency content and indicates the predominance of a frequency shift in the onset of PS from the NeoT group compared to seizures originating from other regions. HFD showed no changes for MT onset PS but marked increases for seizures originating from other regions. SampEn responses were very similar to LZC in all groups. PermH shows a marked decrease for MT onset PS but inconsistent results for other regions. CJS is not very specific for the early periods of the seizure IC1, and shows decreases later during IC2 except for the NeoT group. Measures can also be grouped by their relative responses. Figure 1 summarizes selected results for the MT and NeoT groups illustrating the relative ability of each method to detect the onset of PS and the ability to differentiate the region of onset. Each oval is centered on the mean level change occurring within 8 seconds of PS onset for MT onset patients (x-axis) and NeoT onset patients (y-axis). All measures are normalized to the standard deviation of a baseline period taken a minute prior to onset, and each oval horizontal and vertical dimension represent the standard error of the mean for the MT and NeoT group respectively. Methods whose oval is on the axis (x or y) cannot detect changes occurring at the onset of the seizures from MT or NeoT patients respectively. Oval on the diagonal cannot differentiate between MT and NeoT onset.

Conclusions: The changes of properties of the EEG signals at the onset of PS are often complex and also involve changes in amplitude and frequency content. The most consistent measure to assess and therefore detect the onset of a partial seizure is the GAD signal complexity; however for the purpose of differentiation of the onset zone, a combination of GAD with other complexity (LZC, HFD) or entropy measures (SpEn, SampEn) might prove valuable.

NIH NS48222

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1.120

CURRENT DIPOLE SOURCES OF ANTERIOR TEMPORAL SPIKES: EFFECTS OF ORIENTATION ON CLINICAL FACTORS

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Rationale: The analysis of spike voltage topography revealed two distinct patterns of temporal spikes of type I and type II. The application of source modeling techniques revealed that the orientation of current-dipole sources (O-CDS) of type I spikes was vertical or oblique, while that of type II spikes was horizontal. The correlation of the types with clinical data and intracranial EEGs suggest that type I spikes were more associated with medial temporal lobe epilepsy (m-TLE) than type II spikes. The purpose of this study is to identify the effects of O-CDS of anterior temporal spikes on the clinical factors including intractability, semiology etc.

Methods: We examined the scalp EEGs of 25 epilepsy patients who had anterior temporal spikes. The patients included 13 females, with a mean age of 38.72 ± 14.96 years (mean ± SD). We recorded the EEGs using a 32-channel digital EEG machine, and 21 or 25 electrodes placed on the scalp according to the international 10-20 system. We averaged 10-20 typical spikes in each patient to get an averaged-spike in each patient. We applied a spatiotemporal dipole model to determine O-CDS of the averaged spikes. We divide the patients into two subgroups 'oblique group' and 'horizontal group' according to the O-CDS of single or primary dipole. The current-dipole sources which have the polar angle over 30 degree were considered as oblique dipoles, and those with polar angle below 30 degree were as horizontal dipoles. Definition of drug resistance was the failure of two appropriate antiepileptic drugs and no more than one-year seizure-free hiatus at last follow-up. Clinical factors including age, onset age, disease duration, febrile convulsion, image finding, number of AED, drug response, extra-temporal or neocortical-temporal semiology, secondary generalization, and number of current-dipole sources were compared between two groups.

Results: The current-dipole sources of the averaged spikes were explained by a single dipole in the 17 patients and two dipoles in 8 patients. Sixteen patients are in oblique group and 9 patients are in horizontal group. The extra-temporal or neocortical-temporal semiology were significantly more in horizontal group than oblique group, but no other factors are significantly different between two groups. The 1 of 16 patients of oblique group and 5 of 9 patients of horizontal group had extra-temporal or neocortical-temporal semiology. The tendencies of drug-resistance and polytherapy of AEDs were observed more in oblique group than horizontal group.

Conclusions: The O-CDS of anterior temporal spikes may be associate with the semiology of epileptic patient. The horizontal O-CDS may be more associated with the extra-temporal or neocortical-temporal semiology than the oblique O-CDS. In addition, the oblique O-CDS have tendency to be associated with drug resistance and polytherapy AEDs of the epileptic patients with anterior temporal spikes. Our study suggests that the oblique O-CDS of anterior temporal spikes may be an electrophysiologic marker of intractable mesial-temporal lobe epilepsy.

1.121

CONTINUOUS HIGH FREQUENCY ACTIVITY IN MESIAL TEMPORAL LOBE CONTACTS: POSSIBLE ROLE AS A NEUROPHYSIOLOGICAL MARKER OF EPILEPTOGENICITY

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Rationale: It has been previously described that the major amount of HFOs (ripples, R and fast ripples, FR) is displayed by the mesial temporal lobe contacts. Moreover, we noticed, in some mesial temporal contacts, a peculiar pattern characterized by a continuous/semi-continuous R activity. This makes difficult both to mark the single oscillations, to define in these contacts the background epochs (BKG) and, therefore, to use the automatic HFOs detectors that use the BKG epochs as reference. We studied, in a population of 24 patients implanted consecutively in the mesial temporal structures, the inter-spike BKG activity, evaluating the presence of distinct groups of limbic oscillations and the correlations with different electro-clinical and neuro-radiological variables.

Methods: 24 patients implanted in the mesial temporal lobe structures were studied. Depth electrodes were directed orthogonally in the anterior (Amygdale), mid (Hippocampus, Hp), and posterior locations (Para-Hippocampus). Wakefulness 5 minutes and slow-wave sleep 10 minutes epochs were acquired (500 Hz low-pass hardware filter,

sampling rate of 2000 Hz). We define as BKG the inter-spike Stereo-EEG segments preceding and following each spike with at least 1 sec pre- and post-spike separation. We collected epochs totaling 30 sec per channel. We visually classified the BKG epochs selected in Continuous/Semi-Continuous (C\SC), Irregular and Sporadic (depending on the length of the oscillations and on the presence or not of a clear cut separation between the transient elements, fig.1) and also visually marked the R and the FR elements.

Results: 96 mesial temporal lobe channels were evaluated. The C/SC pattern was found in 34 channels in sleep (35%) and 29 channels in wake (30%). Statistical analyses disclosed a significant concordance between the distribution of the different BKG patterns in sleep and wakefulness ($p<0.001$). Significant relationships were found between the C\SC pattern and the localization of the contacts in Hp regions ($p<0.002$) and the seizure-onset channels (SOZ) ($p<0.002$) (fig.2). Conversely, no significant correlation was found between this BKG pattern and the channels in the lesional zones and the ones with the higher spike rates. Significant relationships were finally found between the higher R rates and the localization of the channels in the Hp and the presence of a C/SC pattern.

Conclusions: the C/SC pattern was found in an important proportion of mesial temporal lobe channels and its presence could have a role as a marker of epileptogenicity (significant relationship with the SOZ channels and correlation with the channels with the higher rates of HFOs). The significant concordance in the distribution of the different BKG patterns between sleep and wake is in keeping with the hypothesis that the presence of the different patterns could be considered as an intrinsic characteristic of the tissue in the particular patient. Its presence, above all, could cause significant problems and bias in the automatic detection of the HFOs.

Supported by CIHR MOP-10189

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1.122

COMPARISON OF ELECTROPHYSIOLOGICAL AND ELECTRO-CORTICAL MAPPING IN IMPLANTED EPILEPTIC PATIENTS

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Rationale: The aim of this project was to compare the localization of language, motor and sensory cortices sites using three different methods; intracranial evoked response potentials (iERP), gamma frequency analysis using the SIGFRIED procedure (Bruner et al. 2009; Schalk et al., 2008) and direct cortical stimulation (DCS) mapping . Each technique was performed on adult epilepsy patients with subdural electrodes implanted over sensory-motor and language cortex for localization of intractable epilepsy.

Methods: In the first method the intracranial data were recorded during two tasks, a language mismatch negativity paradigm (MMN) and a somatosensory paradigm. In the MMN paradigm, the patient passively listened to a stream of sounds consisting of frequent and infrequent stimuli which were either phonemes, matched non-phonemes or matched tones. In the somatosensory paradigm patients were presented with medial nerve stimulation on the hand. Data collected were then analyzed off line by computing iERPs in the time domain .

The second method, was an on-line analysis of the signal in the gamma frequency domain using the SIGFRIED procedure, while the patient performed language and sensory-motor tasks.

The third method was an on-line causal mapping protocol which consisted of a systematic evaluation of the language and sensory-motor functions while the patient received DCS.

Results: The results revealed good spatial overlap for iERPs, frequency analysis and DCS for both the language sites and sensorimotor sites. We also noted that iERPs showed more diffuse activations than was observed using the SIGFRIED analysis.

Conclusions: In conclusion both iERP and SIGFRIED analysis may be useful in identifying essential functional cortical sites, although the distribution may be more widespread compared with DCS mapping.

1.123

AUTOMATIC DETECTION OF NON-CONVULSIVE STATUS EPILEPTICUS

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Rationale: The urgent need to detect and treat Non-Convulsive Status Epilepticus (NCSE) in patients with coma or altered behavior has been widely recognized. The objective is to develop automatic EEG analysis tools for use on unconscious or comatose patients in hospital ICU and emergency departments. Their purpose is to monitor brain state and provide warnings, by analysis of EEG, that the patient's brain is in a potentially dangerous state of NCSE.

Methods: The proposed hybrid system is a combination of two Artificial Neural Networks (ANN) and rule-based algorithms. ANN-1 is trained to detect paroxysmal epileptiform activity in 1-sec epoch and distinguish it from various non-epileptiform EEG patterns and artifacts. ANN-2 is trained to classify 1-minute EEG characteristics or EEG states. In order to enhance ANN-2 detection of NCSE we have included four other EEG states (SLOW, FAST, BSP and ARTIFACT) that are either commonly seen in EEG from patients in coma, or need to be distinguished from the epileptiform activity seen in NCSE. Of these states, the most frequently observed is SLOW, with theta or delta activity. FAST is associated with higher frequencies such as alpha-beta activity. BSP (burst suppression) indicates severe depression of brain function in coma. Artifacts need to be detected to avoid errors in classification of EEG states.

Results: The developed algorithms were tested on recordings ranging from 3 hours (Patient # 4) to 84 hours (Patient # 5). The total of 241 hours (14479 minutes) of EEG data was recorded from 10 patients. These recordings include 5 comatose patients and 5 patients admitted for long term epilepsy monitoring. First four patients were diagnosed clinically and electroencephalographically as NCSE. Patient #5 was an ICU patient in coma without signs of NCSE and the length of study was approximately 4 days. Patients 5-10 were used to evaluate the classifier's specificity and false positive rate. One minute epochs from 9 training and 10 test records were expertly scored into one of the five

EEG states listed above. Training of both ANNs was done using 9 EEG records from patients not included in the test set. Out of 14479 minutes of EEG, 2883 minutes were marked by expert as NCSE minutes. The algorithm correctly classified 2762 NCSE minutes (Sensitivity = 95%) and 11175 non-NCSE minutes (Specificity=96%). NCSE by an often-accepted definition lasts at least 30 minutes. Figure 1 is a running sum of the proportion of one- minute NCSE detections in a 30-minute window from 10 patients. Note that the 4 NCSE recordings exceed 23 detections/30-minute window most (78%) of the time. In contradistinction, the 6 non-NCSE patients showed only brief periods of paroxysmal activity, never exceeding 21/30 (0.7). The separation of NCSE from non-NCSE patients was surprisingly robust, given the small size of the training data set and the lack of full optimization of the detection algorithm.

Conclusions: These findings suggest the potential for highly accurate detection of NCSE in the unconscious or comatose patients. (Partially supported by NIH/NINDS SBIR Grant R44NS039214).

IMAGE: images/905885_A.jpg

Figure 1. NCSE detection for 10 patients. Horizontal red line represents the threshold of 0.8. Patients 1-4 are NCSE patients, patients 5-10 were expert-scored as not NCSE. Patient #5 recording is shown in four separate 24-hour graphs. Patient#1's NCSE has been stopped at 600 min with antiepileptic drug. Blue vertical bar corresponds to the end of the each patient's recording.

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STATISTICAL MAPPING OF ICTAL HIGH-FREQUENCY OSCILLATIONS IN EPILEPTIC SPASMS

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Rationale: Recent studies of humans and animal models of epilepsy have suggested that paroxysmal high-frequency oscillations (HFOs) with frequencies of 80 Hz or greater have a close relation to generation of seizures. It has been hypothesized that cortical sites showing faster HFOs may be particularly significant. It remains to be statistically determined whether HFOs with faster frequencies occur prior to those with slower frequencies at seizure onset. It is also uncertain how HFOs drive or are driven by seizures. In the present study, the spatial and temporal characteristics of HFOs were assessed in relation to the onset of clinical seizure manifestation.

Methods: We studied 11 children with epileptic spasms undergoing extraoperative subdural ECoG recording and assessed 636 epileptic spasms. Electrocorticography (ECoG) signals were sampled from 1,308 cortical sites, and the dynamic changes of HFOs were animated on each individual's three-dimensional MR image surface.

Results: Visual assessment of ictal ECoG recordings revealed that each spasm event was characterized by augmentation of HFOs (Figure 1A). Time-frequency analysis demonstrated that ictal augmentation of HFOs at 80-200Hz was most prominent and generally preceded those at 210-300Hz and at 70Hz and slower (p=0.02). Recruitment of HFOs in the Rolandic cortex preceded and persisted at the clinical onset objectively visualized as electromyographic deflection (Figure 1B). The presence or absence of ictal motor symptoms was related more to the amplitude of HFOs in the Rolandic cortex than in the seizure onset zone (p=0.001). In a substantial proportion of epileptic spasms, seizure termination began at the seizure onset zone and propagated to the surrounding areas; we referred to this observation as the "ictal doughnut phenomenon" (Figure 1C). Univariate analysis suggested that complete resection of the sites showing the earliest augmentation of ictal HFOs was associated with a good surgical outcome (p=0.015).

Conclusions: Our study suggested that HFOs at 80-200Hz in the Rolandic area play a role in determining seizure semiology in epileptic spasms. Our study using macro-electrodes failed to demonstrate the presence of a hierarchy process where ictal HFOs at 210-300Hz drive those at 80-200Hz, but rather demonstrated that HFOs at 80-200Hz preceded those at 210-300Hz.

IMAGE: images/904752_A.jpg

(A) Ictal ECoG traces in patient #4 (2 year 6 months old boy) are shown. Low-frequency filter: 53Hz. High-frequency filter: 300 Hz. Ictal augmentation of ripple-band HFOs occurred at channel #1 and gradually involved the surrounding channels. The offset of ripple-augmentation occurred at channel #1 and gradually involved the surrounding channels. The trigger point for time-frequency analysis was placed at the EMG onset (right deltoid muscle). (B) Time-frequency plots derived from 62 spasms are shown. Augmentation of ripple-band HFOs preceded the EMG onset (denoted as ±0 msec). (C) The amplitudes of ripple-band HFOs associated with spasms are shown.

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A COMPARISON OF DIPOLE SOURCE ANALYSIS AND VISUAL SCALP EEG INTERPRETATION

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Rationale: Historically, the localization of interictal and ictal sources has primarily relied on visual inspection of scalp EEG traces. Identification of the source is based mainly on the assumption that the source underlies the most prominent negative activity. With the advent of modern computer-assisted techniques such as dipole source modeling, more quantitative methods are now available to localize EEG activities. The objective of this study was to compare the results of dipole source analysis and visual analysis of scalp EEG in surgical epilepsy patients

Methods: Non-invasive scalp EEG's from 24 surgical epilepsy candidates were analyzed using the Brain Electrical Source Analysis (BESA) software, developed by MEGIS Software. Scalp EEG was recorded using 10-20 international system with placement of additional electrodes at F9/F10 and P9/P10 for more accurate dipole source localization. EEG activity was digitally recorded referentially to midline electrodes. Continuous monitoring with digital video and EEG was performed using the Nicolet digital video/EEG system. A single neurophysiologist performed dipole source analysis on interictal and ictal waveforms using BESA. Both individual and averaged waveforms were analyzed. Principle Component Analysis was used to separate potential concurrent sources. EEG localization by visual inspection was done independently by two neurophysiologists. The BESA results were compared to the two EEG results for agreement of localization, and were categorized as being in agreement ("concordant"); somewhat in agreement, but with dipole analysis providing further localizing information, ("concordant plus"); or in complete disagreement ("discordant").

Results: Up to 15 interictal spikes and 3 seizures were analyzed for each patient. In total, 41 seizures were analyzed. Compared to the first set of EEG localizations, concordance rate with dipole source modeling results was 34.4%, concordance plus rate was 29.5%, and discordance rate was 36.1%. Compared to the second set of EEG localizations, concordance rate was 27.9%, concordance plus rate was 41.0%, and discordance rate was 31.0%. A Kappa test for inter-rater reliability was done for the two EEG data sets and showed substantial agreement for interictal spikes (kappa 0.612, $p < 0.001$), moderate agreement for seizure sets 1 and 2 (kappa 0.599, $p < 0.001$; and kappa 0.53, $p = 0.003$, respectively), and substantial agreement for seizure set 3 (kappa 0.63, $p = 0.005$).

Conclusions: The results of this study suggest that dipole source modeling may have further localizing value over visual inspection of EEG alone. There was a surprisingly high rate of discordance between dipole source analysis and visual EEG localizations (approximately one-third with both data sets). Furthermore, in the remainder when there was concordance, in a significant percentage, the dipole source analysis provided further localizing information that was not readily apparent by visual inspection alone. Overall, this study suggests that dipole source modeling may play a valuable role in the seizure localization.

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FEASIBILITY OF FOCUSED NEUROSTIMULATION USING INJECTED CURRENTS FROM SCALP ELECTRODES

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Rationale: We investigate the feasibility of noninvasive focal stimulation of brain tissue through simulation studies by examining the effects of small amounts of injected currents from scalp electrodes on an anatomically realistic head and brain model.

Methods: We constructed a realistic finite element model of the human head built from segmented MR images. The model included 11 different tissue-types, including, CSF, gray and white brain matter, soft and hard skull bone, muscle, fat, scalp etc. The model resolution was 2x2x3.2 mm and the model extended from the top of the head to the cervical-dorsal junction. We simulated a 9x9 scalp grid electrode array over the left temporal area with an interelectrode spacing of 2.0 cm. The central electrode was set at -1.0 volt while the outer electrodes were set at +1 volt. The flux densities were computed in the whole head model with an adaptive finite element solver. The published tissue conductivity values were used for simulation studies. For a comparative analysis, a two electrode model over the left temporal area was also simulated. Electrodes were placed 6 cm apart and had +1 volt on one electrode and -1 on the other electrode. The flux densities were plotted and analyzed in various tissues of each slices.

Results: For the grid electrode arrangement, the majority of the currents were confined in an area slightly larger than the electrode grid size. This was observed from the scalp up to a depth of 3 cm in the head where the electrode grid was located. An average volume current density of about 5 microamps/(cm3) was observed in the brain tissue. For the two electrode system, the currents were spread in a large volume of the brain tissue and were not as focused as compared to the grid electrode system.

Conclusions: These preliminary results demonstrate the feasibility of selectively localizing stimulating currents to a restricted volume of the brain based on a careful consideration of the size and configuration of stimulating scalp electrode arrays. The amount of stimulating current is similar to that injected routinely for impedance measurements during routine standard EEG recordings.

1.127

PREDICTION OF EPILEPTOGENESIS AFTER STATUS EPILEPTICUS IN A LITHIUM PILOCARPINE MODEL

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Rationale: There are many acute cerebral insults that lead to the development of chronic epilepsy in some, but not all, people who suffer from such insults. There is considerable interest in the development of antiepileptogenic drugs, and some progress has been made at identifying such agents. If a reliable predictor of epileptogenesis could be developed that would identify people susceptible to develop chronic epilepsy after brain insult, this would allow for early prognostic treatment by use of prophylactic drugs in just these patients. As a first step towards this end, in this study, we have used nonlinear synchronization techniques to evaluate continuous (over months) electroencephalographic (EEG) recordings in rats with chronic epilepsy induced by the lithium/pilocarpine model of status epilepticus and compared the results of the analysis with the ones obtained from rats that do not develop epilepsy (control rats). The hypothesis we tested was that progressive changes in network synchronization of EEG are predictive of epileptogenesis.

Methods: Adult male Sprague-Dawley rats were used in this pilot study. All rats were implanted with an array of 10 Tungsten microwires targeting the cortical and the deeper structures of the limbic region. SE was induced by 3 mmol/kg intraperitoneal lithium chloride followed 24 hrs later by 30 mg/kg pilocarpine subcutaneously. EEG was continuously recorded and the rats were divided into two groups based on the EEG stage when their SE was stopped: Group 1-SE EEG stage III, which is a marker for a less severe brain insult; rats treated at this stage have a lower probability of developing epilepsy, and Group 2-SE EEG stage V, which is a marker for a very severe brain insult; rats treated at this stage have a higher probability of developing epilepsy. Continuous EEG recording was then carried out over 10 weeks in all rats that survived the initial insult of SE to verify the time of onset, frequency, and duration of spontaneous seizures. The analysis of EEG using nonlinear dynamics was performed retrospectively. The average measure of synchrony across all EEG channels was monitored over time until the rats developed chronic epilepsy.

Results: We observed a long-term monotonic trend towards synchronization over a 5 week period (See Figure 1 and caption) following the initial SE episode and prior to development of chronic epilepsy in all the rats in Group 2. On the contrary, rats from Group 1 did not show a monotonic increase in synchrony during the same time period. We believe that this trend in network synchrony can be followed in real-time and be used as a marker for epileptogenesis.

Conclusions: In summary, we have preliminary results that suggest a way to use computerized analysis of EEG recordings to predict which animals will develop epilepsy after SE. This approach constitutes a first step in identifying EEG-based biomarkers of epileptogenesis and could then be used to predict epileptogenesis after traumatic brain injury (TBI) in human patients.

IMAGE: images/908395_A.jpg

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PREDICTING EPILEPTIC SEIZURES BASED ON SURFACE EEG ANALYSIS

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Rationale: Due to the difficulties with scalp EEG analysis including the effects of different types of artifacts and noise, most previously proposed methods for epileptic seizure prediction have been based on the intracranial recordings, and are therefore less clinically applicable. In this study, we propose two novel real-time algorithms, a wavelet-based (WB) and a zero-crossing-based (ZCB), to predict epileptic seizures using surface EEG and compare their results.

Methods: With ethic approval, we applied the seizure prediction algorithms on ~34 hours of multi-channel scalp EEGs from 6 patients with focal epilepsy, recorded in Vancouver General Hospital, BC, Canada, with a sampling frequency of 256 Hz. The dataset included 27 seizures and was visually inspected by an electroencephalographer to determine the electrographic seizure onsets. EEGs from different channels were segmented into 32-second epochs with 50% overlap.

The ZCB method is based on the analysis of intervals between the EEG positive zero crossings, i.e. crossing the zero level when moving from negative to positive values. The histogram of these intervals in each EEG epoch is computed, and the distribution of specific bins, selected based on interictal and preictal references, is estimated using the related histogram values from the current epoch and epochs of the last 5 min. The resultant distribution for each selected bin is then compared to two reference distributions (interictal and preictal), and a seizure prediction index is developed for the current epoch. Comparing this index with a patient-specific threshold for all EEG channels, a seizure prediction alarm is finally generated.

The WB approach, on the other hand, is based on the probability distribution of the EEG relative energy in selected frequency bands, showing statistically significant difference between interictal and preictal references. The current epoch is decomposed by the wavelet packet transform (WPT), appropriate to analyze non-stationary signals such as EEG, using Daubechies-6 wavelet. The energy of each frequency band is computed using the corresponding coefficients in the last decomposition level and divided by the total energy. Similar to the ZCB method, the distribution of the relative energy of each band is then estimated and compared to the reference distributions to calculate the prediction index for each channel and finally generate an alarm.

Results: Applying the proposed algorithms on the epilepsy data, the WB and ZCB revealed, respectively, average sensitivities of 77% and 88% along with average false prediction rates of 0.26/h and 0.22/h (see Table 1). A prediction alarm was considered true if a seizure happened within 40 min after the alarm; otherwise, it was a false alarm. Figure 1 shows the distribution of the prediction time for the predicted seizures.

Conclusions: The proposed seizure prediction methods are able to forewarn the upcoming seizures well in advance. Compared with the ZCB, the WB resulted in less accuracy, showing that energy may not clearly reflect the EEG underlying dynamics.

Table 1. Results of applying the WB and ZCB methods to the epilepsy dataset. Following a leave-one-out cross-validation testing scheme, each recording of a patient was analyzed, while the remaining recordings of the same patient were used as a training set.

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IMAGE: images/900381_A.jpg

Figure 1. Distribution of the prediction time for the seizures predicted by each method. The prediction time for each seizure is defined as the time difference between the prediction alarm and the electrographic seizure onset.

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ESTIMATION OF NEURODYNAMIC MODULATIONS IN THE PRE-ICTAL INTERVAL: AN INFORMATION THEORETIC APPROACH

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Rationale: Seizures are abnormal neurophysiological events which cause a characteristic hyper-synchronization of brain networks as

they evolve. There is evidence that at least for some types of seizure, related neural activity begins to modulate networks minutes if not hours prior to clinical onset. However, consistent and robust estimation of seizure precursors from electroencephalograms (EEG) has

proved to be a difficult problem. In addition to the inherent variability of EEG signals, seizure heterogeneity and limited specificity of some proposed measures of precursory activity may significantly affect the accuracy of seizure prediction. Information theory provides an attractive framework for estimating potential pre-ictal network coordination using probabilistic measures.

Methods: We estimated information theoretic parameters of interaction between networks from pre-ictal and ictal EEGs from 7 patients with multiple focal seizures, with temporal or frontal onset. These parameters included time-dependent mutual information, conditional entropy and net information. We also estimated corresponding measures from baseline EEGs, clinically identified as non-seizure related. A total of 36 seizures were analyzed and at least two baseline segments from each patient at two spectral intervals, below and above 100 Hz, respectively.

Results: Information theoretic parameters, including relative and conditional entropy and mutual information estimated from high-frequency EEG, were specifically modulated in the pre-ictal interval. These parameters were statistically identical to those in the ictal interval, but distinct from baseline. In contrast, corresponding lower-frequency parameters varied non-specifically between the three intervals. Mutual information and conditional entropy in the pre-ictal interval monotonically increased, in the same way as during the ictal interval, particularly in frontal seizures, which suggests that brain networks may become increasingly hyper-synchronized prior to seizure onset.

Conclusions: Resting brain networks are specifically modulated prior to clinical seizure onset. Information theoretic parameters quantify precursory neurodynamic changes in the high-frequency EEG, and may be thus be used for seizure prediction. In contrast, lower frequency network interactions change non-specifically at baseline and pre-ictal

intervals and may, therefore, not be robust measures of seizure-related precursory neural activity. These findings have important implications for next-generation therapeirs in epilepsy, particularly for the optimization of automated seizure prevention and drug-delivery systems.

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SYNCHRONY IN NORMAL AND FOCAL EPILEPTIC BRAIN: THE SEIZURE ONSET ZONE IS FUNCTIONALLY DISCONNECTED

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Rationale: Synchronization of local and distributed neuronal assemblies is thought to underlie fundamental brain processes such as perception, learning, and cognition. In neurological disease, neuronal synchrony can be altered, and in epilepsy it may play an important role in the generation of seizures. Multiple studies have reported that epileptic brain is characterized by increased neuronal synchrony, except possibly prior to seizure onset when synchrony may decrease. Previous studies using intracranial EEG, however, have been limited to patients with epilepsy.

Methods: We investigate neuronal synchrony in epileptic and control brain using intracranial EEG recordings from patients with medically resistant partial epilepsy and control subjects with intractable facial pain. Linear cross-correlation and mean phase coherence of local field potentials (LFP) are used to measure neuronal synchrony.

Results: For both epilepsy and control patients, average LFP synchrony decreases with interelectrode distance. Interestingly, we find that control patients have greater average LFP synchrony than patients with epilepsy. The difference in average synchrony between control and epileptic brain is shown to be from the functional disconnection of the epileptic brain region generating seizures from surrounding brain. Synchrony between electrode pairs bridging seizure generating brain and other regions was significantly less than between other electrode pairs in the epileptic brain and control brain. With greater activity in a seizure generating region, there is less synchrony with neighboring tissue outside that region.

Conclusions: We propose that the region of epileptic brain generating seizures is functionally isolated from surrounding brain regions. We further speculate that this functional isolation may contribute to the spontaneous generation of focal seizures, and it could be a clinically useful electrophysiological signature of epileptic brain.

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ACCURACY OF DENSE-ARRAY EEG SOURCE ESTIMATION OF INTERICTAL DISCHARGE IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Rationale: Dense-array EEG is consisted with up to 256 channel electrodes which increase spatial resolution and recently has been used in epilepsy monitoring. This study is to evaluate the accuracy of electrical source estimation of interictal discharge by dense-array EEG as compared to simultaneously recorded intracranial EEG.

Methods: Three patients with medically refractory temporal lobe epilepsy underwent invasive monitoring after conventional LTM. Patients are as the followings. Case1: tumor in the right amygdala, Case2 : left hippocampal sclerosis, Case3 : no lesion on MRI. The total of 52-62 channel subdural electrodes was placed over the mesial and lateral temporal lobe. We conducted dEEG recording by Geodesic Sensor Net (Electrical Geodesics Inc.EGI) for 4-7 hours with intracranial EEG at 1 kHz sampling simultaneously. Then intracranial spikes were categorized based on its location and analyzed with dense-array EEG using GeoSource, the electrical source estimation software which applied a local autoregressive average (LAURA) to provide source estimates of the three dimensional cortical distribution of current density for dense-array EEG.

Results: All cases showed the interictal discharges originating from mesial and lateral temporal region independently. Dense-array EEG also detected some of these interictal discharges and its source estimation was localized in the similar region to the intracranial EEG.

Conclusions: Dense-array EEG used in conjunction with electrical source analysis can be a powerful tool in epilepsy monitoring as it shows excellent accuracy of source estimation noninvasively.

IMAGE: images/907221_A.jpg

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EPILEPTOGENICITY INDEX IN BITEMPORAL EPILEPSY

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Rationale: Some patients suffer from bitemporal epilepsy which is an unfavorable condition as surgery is contra-indicated and few therapeutic options can be proposed. This retrospective study focused on the precise localization of the Epileptogenic Zone (EZ) in patients suffering from bitemporal epilepsy, to determine in particular the relative involvement of hippocampal and peri-hippocampal regions in this kind of epilepsy.

Methods: All patients displaying bitemporal epilepsy, and explored by Stereo-Electro-Encephalography (SEEG) in our centre, were analysed. Bitemporal epilepsy was defined as : 1) simultaneous seizure onset in both temporal lobes, and/or 2) independant seizures arising from right and left temporal lobe, and both recognized by the patient as usual seizures. The seizures recorded during SEEG were either spontaneous seizures or stimulation-induced seizures. We analysed ictal EEG of all recorded seizures in our patients and we used the 'Epileptogenicity Index', a method previously described (Bartolomei et al, Brain 2008 Jul;131(Pt 7):1818-30 ; Aubert et al, Brain 2009 Nov;132(Pt 11):3072-86) that accounts for both the propensity of a brain area to generate rapid discharges and the time for this area to get involved in the seizure. These results were compared with those of patients suffering from

unilateral temporal epilepsy, but who had temporal electrodes bilaterally implanted during the SEEG.

Results: In patients with bitemporal epilepsy, EZ encompassed both subhippocampal regions (perirhinal, entorhinal cortices) and hippocampi.

Conclusions: This study raises the question of whether the involvement of these subhippocampal regions may be a pejorative prognostic factor (higher risk for the development of bitemporal epilepsy ?). It also helps in delineating the EZ in these peculiar form of epilepsy and could be useful for the determination of the most appropriate target for non-surgical procedures such as chronic temporal lobe stimulation, in the future.

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IDENTIFYING EPILEPTOGENIC TUBERS WITH BESA AND LORETA—A STUDY OF NON-INVASIVE INTERICTAL EEG SOURCE LOCALIZATION

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Rationale: Given the complexity in the identification of the epileptogenic tubers in patients with tuberous sclerosis complex (TSC), we continue our efforts in seeking additional non-invasive tools to improve the localization accuracy of surgical targets.

Methods: Retrospective data from 9 children (ages 0.92-10.42 years old, mean 3.71 years old; 4M:5F) with intractable epilepsy from TSC were analyzed. All children underwent epileptogenic tuber resection in 2003-2010 with seizure freedom in all but 2 who became seizure free after a second operation (follow up 0.25-5.67 years). Their surgical evaluation included scalp EEGs (ictal and interictal), MRI, FDG-PET, and MSI. We used a dipole fitting model (BESA) and a distributed source model (LORETA) to study the pre-surgical digital EEGs (21 channels 10-20+T1-T2). Interictal spikes were automatically searched and classified according to morphology and topography, which were then visually screened, artifact excluded, and averaged, without prior knowledge of surgical evaluation localization results. The resultant localization maps were then compared to the eventual ECoG-guided surgical site.

Results: Between 9 children, 11 interictal EEG studies were analyzed. The length of useful EEG segments for analysis ranged between 52 minutes and 8h 14 min. The total number of spikes captured for each patient ranges from 34 to 3273 with a mean of 1567. The number of spike clusters for each study ranges from 2 to 8. The average number of spikes in each cluster for each patient ranges from 17 to 1383. With BESA, the weighed proportion of clusters in the resection site ranges from 10% to 100% (overall 61.0%). With LORETA, the weighed proportion of clusters in the resection site ranges from 11% to 100 (overall 57.7%). For clinical relevance, we define 4 categories: A) All clusters overlap with the resection site. B) >=50% of the clusters overlap with the resection site. C) <50% of the clusters overlap with the resection site. D) No clusters overlap with the resection site. With BESA, the number of studies in category A/B/C/D is 3/7/1/0, while that for LORETA is 3/5/3/0.

Conclusions: In the majority of our patients, either BESA or LORETA can accurately identify the more active lobe. Compared with the interictal or ictal EEG reports, the computer-assisted cluster analysis offers an objective and quantitative measure of the relative importance of each cluster using number of spikes. Moreover, BESA can be used to breakdown spikes into sequential time-dependent components. In one patient with modified hypsarrhythmia, BESA correctly identified the lobe of onset despite the more obvious expression on the opposite side with no clear asymmetry by visual interpretation. Overall, these tools are not yet validated to be clinically practical. However, given that they are non-invasive with relatively low-cost and no risk to the patients, they may be refined to become adjunctive tools in pre-surgical evaluation of children with epileptogenic tubers.

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DYNAMICS OF FREQUENCY FLOW DURING TEMPORAL LOBE EPILEPTIC SEIZURE

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Rationale: EEG data during temporal lobe seizures have been reported to show lateralized buildup of theta (4-7Hz) activity following a period of generalized attenuation near the seizure focus with loss of awareness. However the exact dynamics of the theta activity, and clinical significance of such a buildup is not known.

Methods: Ictal and baseline EEG data from 9 patients with temporal lobe epilepsy were analyzed using wavelet based algorithm to study the frequency flow dynamics.

Results: We found that prior to onset of seizure; the frequency flow gradually builds up to 5-12Hz range at the focus and at distant channels unlike during baseline conditions of the same patients. Using wavelet based method we could analyze frequency flow dynamics instantaneously from rapidly changing EEG signals.

Conclusions: Although the exact significance of frequency buildup is not clear, it is interesting to note that the buildup is seen not only at the focus but also at distant channels and is clearly different from the baseline conditions. This might suggest that during temporal lobe seizure the neuronal interactions propagate over large regions of the brain even at the very initial stages. Number of subjects in our analysis is small and also this study included only patients with temporal lobe epilepsy. We plan to study more patients with temporal lobe as well as other types of epilepsy including non-temporal and generalized epilepsy to explore whether the same kind of frequency flow dynamics are observed.

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CHANGES IN SYNCHRONY WITHIN NEURONAL NETWORKS MEASURED DURING ELECTROCORTIGRAPHY ACCOMPANY CHARACTER RECOGNITION: A BRAIN-COMPUTER INTERFACE PARADIGM

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Rationale: In development of brain-computer interface methods, a previous study (Shih et al, 2009) determined that the P300 response to

novel stimuli underlies letter discrimination ability in subjects during electrocortigraphy (ECoG) recordings. Localization of the response, however, does not appear to respect traditional neuroanatomic localization, with responses recorded from diverse dominant hemisphere locations. We hypothesize that neuronal networks rather than specific foci underlay visual character recognition.

Methods: Three subjects with intractable epilepsy underwent intracranial subdural and depth electrode recordings. Alphanumeric characters via a 6x6 square matrix were presented to subjects who were instructed to silently count the number of times a target character was highlighted. >100 samples of ECoG recorded from subsets of electrodes were recorded during true character recognition ("+"), false character recognition ("-"), and "base" states without character highlighting. Network activity was measured iteratively for all electrode pairs with the synchrony index (SI), a measure of local amplitude coherence combined with electrode pair phase synchrony linkage. Electrode pairs with SI values falling above or below the 95th confidence limit (determined via t-scores) of the mean difference between (+) and (-) states compared to the base state were mapped and compared to regions previously established as important in the P300 response.

Results: In all three subjects, during (+) states a nexus of relative desynchronization extended beside regions of P300 responses. The same general region of desynchronization, usually more limited in extent, was maintained during (-) states, with emergence of focal regions of hypersynchrony. Regions of hyper- or desynchronization usually did not involve electrodes with consistent P300 responses. In one case with the entire grid available for mapping, the difference between (+) and (-) states was significantly different demonstrating regional hypersynchrony during (-) states. The two other cases that lacked full electrode assessment did not demonstrate significant differences between recognition states.

Conclusions: Regional networks of synchronous neuronal activity may accompany the P300 responses that underlie simple character recognition tasks. Neuronal network properties and the means to quantify their activity may be important in the design of brain-computer interfaces.

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PROPAGATION OF INTRACRANIAL ELECTROENCEPHALOGRAPHIC ACTIVITY BETWEEN NEOCORTEX AND SUBCORTICAL STRUCTURES AS AN INDICATOR OF SEIZURE ONSET

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Rationale: Epilepsy surgery planning can be complicated when intracranial EEG monitoring reveals ictal patterns with a broad regional neocortical onset, particularly if the onset region includes eloquent cortex. In some cases, however, a regional ictal pattern may arise from ictal activity that is propagated from other structures that might be safer to resect. This is most evident when a lesion is present in nearby neocortex or in mesial temporal structures, but may also occur in the absence of a lesion. Recordings from both intracranial depth electrodes and subdural electrode grids can provide crucial information about the propagation of seizure activity between mesial temporal and neocortical networks, and advanced analyses of the propagation of ictal activity between these structures and others may improve localization of the ictal onset zone when planning resection.

Methods: Intracranial EEG recordings obtained during multiple seizures (3-7) were parameterized using multivariate autoregressive models (MVAR), and analyzed with short-time direct directed transfer function (SdDTF), which estimates the direction of flow between electrodes (sites), as well as the intensity, spectral content, and temporal evolution these flows. Seizures were marked at their electrographic onset, and the propagation of activity was analyzed across a wide range of frequencies (0-235 Hz).

Results: SdDTF analyses showed propagation of ictal activity between a limited number of contacts in mesial temporal regions and a larger number of neocortical sites, as well as less prominent flows among the neocortical sites themselves. These findings suggested a prominent role for mesial temporal structures in seizure generation.

Conclusions: For patients undergoing intracranial monitoring for epilepsy surgery, analyses of the patterns of EEG activity propagation between mesial temporal and neocortical networks may provide additional information that can improve seizure localization, in turn optimizing post-surgical outcomes and minimizing post-operative impairments.

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OBSERVATION OF EMERGING ICTAL NETWORK DYNAMICS USING SYNCHRONY INDEX

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Rationale: Surgical resection remains the best option for long term seizure control for patients with medically refractory focal epilepsy. Unfortunately, such treatment does not always result in seizure freedom, particularly in the long term. There is growing evidence that focal seizures may include an ictal network which may develop over time and potentially include more than one zone of seizure onset. Current presurgical evaluation applies structural and physiological imaging to identify the likely seizure onset zone. Improved techniques are required for identification of the complete ictal network both structurally and physiologically, and to establish the role of the primary seizure onset zone within the network. We demonstrate dynamic spatiotemporal changes in connectivity within the ictal network during temporal lobe seizures using a linear measure of synchrony, the Synchrony Index (SI).

Methods: We analyzed intracranial EEG data from 11 seizures from a patient with confirmed hippocampal sclerosis who is seizure free 2 years after resective surgery. A previously reported analysis demonstrated that the visually determined electrodes of seizure onset could be objectively identified using parameters derived from our Synchrony Index. EEG was recorded at 200 samples per second. Using MATLAB, the SI was calculated for every possible electrode pair combination in non-overlapping, one-second bins over the duration of the extracted file. Videos were constructed to dynamically display the highest SI value connection for each electrode for each second beginning 100 seconds preictally and ending 150 seconds after seizure onset. Still images were generated to highlight specific time points.

Results: Dynamic SI changes demonstrated clear spatiotemporal differences between the preictal, ictal and postictal time periods during 9 of 11 seizures. The preictal and postictal periods were dominated by

diffuse, low SI value connections. During seizures, a nexus pattern repeatedly emerged with the electrode of visually determined seizure onset (SOZ) at the center with widespread connections. A large increase in SI value occurred first in the SOZ, then throughout the remainder of the electrodes. This was most persistent 10-20 seconds into seizures, which correlates well with our previously published data showing a large rise in SI value in the SOZ at that time. Overall, this pattern displays a network in which the majority of the recording electrodes are strongly functionally connected to the SOZ.

Conclusions: Techniques for spatiotemporal display of seizure networks are needed to augment our understanding of the pathophysiology of epilepsy and our selection of surgical candidates. We have demonstrated the use of a linear measure of synchrony to display the emergent, dynamic network patterns during a seizure in a manner that objectively highlighted the SOZ. Further investigation is required to refine this approach and improve the analysis and description of this type of data.

IMAGE: images/905776_A.jpg

Time course of typical left hippocampal seizure. (A) Representative left hippocampal onset seizure. Red arrows mark seconds 17-20. (B) Blowup demonstrating transition to higher frequency seizure activity. (LF 1 Hz, HF 70 Hz, Sens 750 ìV p-p)

IMAGE: images/905776_B.jpg

Dynamic ictal network centered on left hippocampal electrode. Pre- and post-ictal periods show diffuse patterns. Ictal period demonstrates emergence of a highly synchronous pattern focused around left hippocampal electrode 2. Dots represent intracranial electrodes. Lines display the strongest SI connection at each second. Number in parentheses is the second relative to ictal onset.

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SOURCE LOCALISATION BASED ON SUBDURAL EEG STUDIES OF FRONTAL LOBE EPILEPSY

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Rationale: Source localisation methods are increasingly applied on scalp EEG signals in clinical practice. However, data on source reconstruction derived from intracranial (subdural) EEG recordings is currently limited to simulation studies and single case reports. We retrospectively implemented novel methods of source imaging in the analysis of ECoG data in an attempt to define the accuracy of inverse solutions, as well as the limitations and feasibility of application in resection planning. The clinical validation of our findings was provided by postoperative outcomes.

Methods: Continuous sleep segments of ECoG data obtained during the invasive presurgical workup of 14 patients with refractory frontal lobe epilepsy were retrospectively reviewed. MRI imaging was either unremarkable or showed poorly delineated hyperintense regions that raised suspicion for unilateral frontal lobe dysplasia. Subdural coverage was variable consisting in a lateral grid and additional intrahemispheric strips in nine cases as well as basal frontal strips in four cases. Spikes were visually identified and marked by two independent reviewers according to amplitude, voltage field and disruption of normal background. Consensus spikes were averaged to serve as a substrate for the realistic boundary element model (BEM) based sLORETA and MUSIC (MUltiple SIgnal Classification) algorithms. Results of source localisation were visualised using T1-weighted MRI data sets acquired prior to and after surgical treatment.

Results: In ten patients a single spike population was identified, while four patients presented multifocal spikes within the frontal lobe. Inverse solutions localised within the semiologically and electroencephalographically presumed epileptogenic zone in all cases with a distance of 0-7 mm between MUSIC and sLORETA maximums. In seven cases total resection of the epileptogenic zone including inverse solution was possible, followed by Engel Ia outcome. In two cases where epileptogenic zone/solution localised within eloquent cortex areas multiple subpial resections were offered that led to Engel IIIa and Engel IVb outcomes respectively. In another three patients with Engel Ia outcome solutions localised at resection border. Finally, in two patients with multiple spike foci and resulting multiple solutions, partial inclusion of solutions in the resection correlated with Engel IIIb and IVa outcomes. Histology showed focal cortical dysplasia in all but one case.

Conclusions: This is the first study evaluating the applicability of source reconstruction methods in subdural recordings and validating results through outcomes of epilepsy surgery. Complementary information derived from the MUSIC and sLORETA algorithms may prove valuable in improving localisation, especially regarding deep sources. This is crucial in the implementation of tailored resections and improvement of clinical outcomes.

1.139

EFFECT OF DURA ON SCALP EEG SIMULATIONS

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Rationale: The dura, which covers the cortical surface, is less conductive than cerebrospinal fluid (CSF) and brain tissue. As a result, the dura restricts the flow of volume of electrical currents originating from brain tissue and traversing the skull and scalp layers. Thus, although scalp EEGs must be severely influenced by the dura layer, this effect has not been previously quantified. The purpose of this project is to examine the effect of dura on simulated scalp EEG.

Methods: We examined the effect of dura with a detailed finite element model of the human head constructed from segmented MR images. The model included 20 different tissue-types, including, CSF, gray and white matter, dura layer, soft and hard skull bone, scalp, muscle, etc. The model resolution was 1x1x1 mm and extended from top of the head to the upper cervical region. The electrical activity was simulated with random dipole distributions in the cortex having a uniform intensity distribution in the range of 0.0 to 0.1 mA. Scalp EEGs were simulated for two head models with an adaptive finite element solver. One model had the dura layer and in the other model, the dura layer was replaced with the CSF.

Results: Spatial contour plots of the scalp potentials over the cranium were constructed. We was found that the inclusion of dura layer reduced the scalp potentials by about 33% as compared to not including dura layer in the model.

Conclusions: For accurate simulation of scalp EEG, the dura layer along with skull bone, should be included in the model

1.140

COMPARISON OF DYNAMIC MEASUREMENTS BETWEEN A COHORTS OF CHILDREN WITH CHILDHOOD ABSENCE EPILEPSY AND CHILDREN WITH PARTIAL SEIZURES

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Rationale: Children with partial seizures differ in their seizure semiology, treatment, and etiology from those with a primary generalized epilepsy like childhood absence epilepsy. Yet there may be similarities, for example, in the poorly understood mechanism of seizure initiation.

The differences in standard EEG between the two groups are stark. Chaotic measurements are another approach that has been used to describe dynamic systems like EEG. Such measurement can be useful in finding unexplained factors in a dynamic system.

Methods: There were 12 children with EEG's meeting the ILAE criteria for childhood absence epilepsy. There were 2 boys and 10 girls. In the partial seizure group there were 20 children. There were 50 seizures selected for the analysis. All data were acquired using Nicolet BMSI hardware to record a 24 channel (EEG) using the international 10/20 of Electrode placement. EEG records were reviewed using 15 mV per millimeter sensitivity with high voltage filter at 15 Hz and low frequency filter set at 1.0 Hz. The F7 channel of the EEG was selected for actual analysis. The EEG seizure data was converted to a .cvs file using Nivue. The .cvs file was read by a MatLab macro and macro for phase space plotting of the seizures. The .cvs file of the seizures was also converted to .dat file for processing by RRChaos to produce the dynamic measures of entropy, eigen values, and for the generation of baseline noise.

Results: There are similarities in the pattern of the dynamic systems measurements. These similarities include a shared Eigen value with seizure onset, complex pattern of entropy changes, and reduced dimensionality. Phase space plots also had similar patterns of development. All these chaotic changes were compared to randomized noise controls and were significantly different.

Conclusions: These chaotic measures have detected similarities in the dynamics of the EEG, despite clinical differences in their EEG's baseline and the abnormalities, molecular and genetic etiologies, and treatments, and outcomes. Given these similarities, these data suggest that there is a common uderlying systems change in the dynamics of the pathophysiology at the onset of their seizures.

IMAGE: images/908305_A.jpg

Eigen value of absence seizure for patient 4.

IMAGE: images/908305_B.jpg

Entropy vaues of absence seizure of patient 4.

1.141

EFFECTS OF VAGUS NERVE STIMULATION ON ELECTROCORTICOGRAPHY

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Rationale: A long-term electroencephalographic(EEG) change caused by vagus nerve stimulation (VNS) as decreasing paroximal waves on EEG has been known, whereas an acute change has not been established so far. However, the high frequency component of EEG has not been considered because of scalp-recorded EEG is unable to detect it. We examined the effect of VNS on electrocorticography(ECoG) in a patient who had been receiving VNS.

Methods: An 11-year-old boy with multifocal intractable epilepsy had VNS therapy for one year. He experienced some reduction of seizure frequency and severity but drop attacks newly appeared. Thus, total callosotomy was performed. During the surgery, cortical electrodes were placed on the bilateral superior frontal gyri and ECoG was recorded with a sampling rate of 2000 Hz. VNS stimulation signal was simultaneously recorded from a cervical skin electrode. Time frequency analysis was performed using EMSE software (Source Signal Imaging Inc. San Diego). We compared VNS-on and VNS-off phases and examined spatiotemporal dynamics of ECoG power in each bands.

Results: Significant increase of power in 250-1000Hz was observed during VNS-on phase starting several seconds after the start of VNS. This reaction could not be attributed to an artifact of stimulation because the change stopped several seconds after the end of VNS.

Conclusions: An acute VNS-induced ECoG change was demonstrated in this single patient. The change was restricted in high frequency bands, and that may be the reason why previous scalp EEG studies failed to detect this change. This VNS-induced augmentation of 'fast-ripple' oscillation may partly explain the inhibitory effect of VNS on the cerebral cortices, since the activity of this band has been suggested to be closely associated with inhibitory interneurons.

1.142

PREDICTING SUCCESS OF VAGUS NERVE STIMULATION (VNS) FROM INTERICTAL EEG

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Rationale: Vagus nerve stimulation (VNS) has shown to be an effective treatment for drug resistant epilepsy in numerous patients. Most long-term studies concluded that more than 50% seizure reduction was accomplished in 20 to 55% of the patients. However, it is still not possible to predict which patients will profit from VNS. In this study, we identify predictive interictal EEG features for seizure reduction after VNS.

Methods: 19 adult patients with medically refractory epilepsy and an implanted VNS system were included. All patients suffered from (multi) focal, medically intractable epilepsy with varying focus locations. Interictal EEG registrations, recorded before implantation, were retrospectively analyzed. Two symmetry measures, the standard Brain Symmetry Index (rsBSI) and the pairwise derived Brain Symmetry Index (pdBSI), were used to predict VNS outcome. Reduction in seizure frequency was used to define the responders to VNS treatment.

Results: 10 Patients obtained a reduction in seizure frequency (responders[0]) of which 7 had a reduced seizure frequency of at least

50% (responders[50]) during a follow-up period of 2 years. On average, we found higher BSI values for delta, theta, alpha and beta bands for non-responders compared with responders. The variance in pdBSI values of the non-responders is in general much larger than in pdBSI values of the responders. rsBSI of the delta and pdBSI of the theta and alpha band could significantly discriminate between responders and non-responders.

Conclusions: Quantifying EEG symmetry using the BSI shows promising results in predicting the reduction of seizure frequency after VNS treatment in adults. BSI values in the different frequency bands support the assumption that patients who will not respond to VNS treatment have more asymmetric spectral characteristics of the interictal EEG than responders.

1.143

CORTICAL GAMMA-OSCILLATIONS MODULATED BY PICTURE NAMING AND WORD READING IN PATIENTS WITH FOCAL EPILEPSY

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Rationale: Identification and preservation of the sites critical for picture naming and reading are clinically important in presurgical evaluation of epileptic patients. Removal of such sites may lead to functional deficits and decreased quality of life in patients with focal epilepsy. We measured the presence or absence of gamma-augmentations in response to two types of visual tasks consisting of picture naming and word reading. Gamma augmentation can be a measure of cortical activation elicited by a task.

Methods: We studied four patients (ages ranging from 9 to 17) with focal epilepsy (three on the left hemisphere and one on the right) who underwent extraoperative electrocorticography (ECoG) recording followed by cortical resection. Patients implanted with extensive subdural grids on the side of the presumed epileptic focus were asked overtly name images presented sequentially in the picture naming task and asked to read and vocalize written words in the reading task. ECoG signals recorded during these tasks were transformed to time-frequency matrices, and the amplitudes of gamma-oscillations at 50-150 Hz were compared to those during the resting reference period. Cortical sites showing statistically-significant gamma-augmentation were identified.

Results: Gamma-augmentation commonly elicited by both tasks was found in the caudal occipital area, bilaterally. Gamma-augmentation commonly elicited by vocalization was found in the Rolandic area, bilaterally. Picture naming tasks preferentially induced more gamma-augmentation in portions of occipital, temporal, and pre-motor areas in comparison to word reading tasks, bilaterally (i.e. these areas were less active during word reading tasks). Likewise, word reading tasks preferentially and selectively induced gamma-augmentation in portions of left parietal area as well as right occipital-temporal area.

Conclusions: Gamma-augmentation measured on ECoG can identify cortical areas commonly and differentially involved in picture naming and reading tasks in patients with focal epilepsy.

1.144

AUTOMATIC SEIZURE DETECTION ALGORITHM BASED ON THE HUMAN VISUAL INTERPRETATION PROCESS OF SCALP EEG

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Rationale: An automatic seizure detection algorithm is important to reduce the workload posed by the large amount of EEG data recorded in an epilepsy monitoring unit. The development of such an algorithm is demanding, due to mainly two factors: the inter-patient variability of seizure characteristics and artifacts contaminating the EEG data. The limitation of the currently available detection systems is their high false detection rate (0.5/h).

Methods: The algorithm presented here extracts features from the EEG, which guide the neurologists visually, when reading EEG data. These features include change in frequency distribution, asymmetry between the hemispheres, morphology characterized by repetitive sharp waves, and evolution in amplitude, frequency and topology. Therefore, the main steps of the algorithm are analysis of power spectral density in different frequency bands, brain symmetry index modified for contralateral channel pairs, extraction of wave segments, and retrieval of a series of repetitive waves with gradually evolving amplitude.

The algorithm was tested on 680 hours of EEG data containing 26 temporal lobe seizures and 95 extratemporal lobe seizures from patients with refractory partial epilepsy, who underwent a presurgical evaluation.

Results: The sensitivity for temporal lobe seizures was 84.4% while for extratemporal seizures 46%. Missed seizures either had short ictal pattern on EEG or were difficult to detect visually as well. The number of false detections was 0.15/h, and were mainly due to rhythmic, low-frequency patterns of sleeping and drowsiness.

Conclusions: Our automatic seizure detection algorithm is able to mimic the visual interpretation of the human observer and can work real-time. It is a sensitive method for detection of temporal lobe seizures, but not extratemporal lobe seizures. An advantage of the algorithm is its high specificity, which could be further improved if sleeping and drowsiness patterns could be excluded.

Seizures which are difficult to detect visually will also be missed by our algorithm. Methods revealing hidden patterns of EEG might be employed for such seizures, before applying the proposed steps of detection.

1.145

CHARACTERIZING PRE-ICTAL AND INTER-ICTAL STATES WITH GRAPH THEORETICAL APPROACHES

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Rationale: Graph-theoretical approaches to a characterization of anatomical and functional brain networks has been a rapidly evolving field recently. Previous studies on epileptic brain networks reported on an increased regularization of network topology during seizures as compared to the pre- and postictal intervals, and an altered functional

brain topology in epilepsy patients can even be observed during the seizure-free interval. However, these studies were based on recordings that lasted from a few seconds to several minutes only. We here investigated the time-course of graph theoretical approaches on the time scales of days particularly with respect to an identification of a pre-ictal state.

Methods: We analyzed invasive multi-day, multi-channel EEG recordings from 13 patients with focal epilepsies undergoing pre-surgical evaluation. Using a moving-window approach (duration of each window: 20.48 s corresponding to 4096 data points; no overlap) we estimated the strength of interactions (via mean phase coherence) between all pairs of sampled brain regions. We defined functional network links by thresholding the interaction matrix and estimated the global network characteristics average shortest path length L and clustering coefficient C.

Results: Both network characteristics exhibited large fluctuations over time, however with some periodic temporal structure. These fluctuations could — to a large extent — be attributed to daily rhythms while relevant aspects of the epileptic process contributed only marginally. Particularly, we could not observe clear cut changes in network states that can be regarded as predictive of an impending seizure.

Conclusions: Global statistical properties of epileptic brain networks strongly reflect daily rhythms and possibly alterations of the anticonvulsant medication. Identification of a possible pre-ictal state with graph-theoretical approaches requires a better understanding of these daily rhythms as well as further methodological developments.

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1.146

CHARACTERIZING DIRECTED INTERACTIONS IN EPILEPTIC BRAIN NETWORKS FROM NONINVASIVE EEG RECORDINGS

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Rationale: We address the question whether directed interactions between brain regions of epilepsy patients differ from those of healthy controls even during the seizure-free interval. Furthermore we investigate whether these differences may help to identify the seizure generating area and whether this area preferentially drives or is driven by other brain regions.

Methods: We analyzed EEG data recorded under a resting-state eyes-open and eyes-closed condition from 23 healthy controls and from 21 epilepsy patients with different cerebral locations of the seizure generating area. We used two approaches to measure directed interactions, namely Granger-causality (GC) and symbolic transfer entropy (STE).

Results: During the eyes-open condition widespread directed interactions could be observed between different brain regions in both the patient and the control group. For the latter group, particularly the occipital regions appeared to preferentially drive other brain regions during the eyes-closed condition. For the patient group, other brain regions exhibited an even stronger driving, and in the majority of cases these driving regions coincided with the approximate location of the seizure generating area. GC and STE detected these driving regions with a different sensitivity.

Conclusions: Our findings indicate that the epileptic focus preferentially drives other brain regions even during the seizure-free interval although this driving appears to depend on the state of vigilance. Relevant information about the seizure generating area and its interactions within the epileptic network can be assessed by analyzing the directionality of interactions.

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CLASSIFICATION OF EPILEPTIC SEIZURES AND EPILEPSY SYNDROMES AT PEDIATRIC LONG-TERM VIDEO-EEG MONITORING UNIT

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Rationale: The etiology and clinical course of epilepsies are very heterogeneous; this has lead to attempts for classification of epilepsies in order to achieve accurate diagnosis and treatment approaches, and determine prognosis.

Methods: 320 patients admitted to our video-EEG monitoring unit between August 2005-December 2007, were reviewed retrospectively; 183 patients with ictal recordings, aged between 3 months-18 years (mean 9.5 ± 4,7 years), were studied. Clinical and etiological features were documented. Patients were classified with respect to epileptic seizures and epilepy syndromes based on ILAE 1981 Clinical and Electroencephalographic Classification of Epileptic Seizures, ILAE 1989 classification of epileptic syndromes and Semiyologic Seizure Classification (SSC).

Results: According to ILAE 1981 Clinical and Electroencephalographic Classification of Epileptic Seizures, ~82% of our patients were classified as having partial seizures and ~18% were classified as having generalized seizures. Partial seizures were significantly higher in patients who were >12 years, compared to the other age groups ($p < 0.05$). According to SSC, 183 patients had 211 different types of seizures; lateralizing features were observed in half of the patients; 114 (54%) seizures showed semiologic evolution. A total of 373 semiologic subtypes were observed in 211 seizures; majority of them were motor seizures (78%, 291/373). Simple motor semiology (49%, 184/373), and tonic seizures (57.6%, 106/184) were the most common semiologic types. According to ILAE 1989 classification of epileptic syndromes, localization-related epilepsies and syndromes were seen in 80.4% (147/183) of patients and 83% (122/147) had symptomatic epilepsy. Patients with extratemporal lobe epilepsies constituted 54.4% of patients with localization-related epilepsies. Overall malformations of central nervous system (CNS) were seen in 29.5% of patients as the leading etiologic factor.

Conclusions: Semiologic Seizure Classification provided more detailed information compared to ILAE 1981 epileptic seizure classification to help determine the epileptogenic zone. Our results, albeit patient

selection bias, emphasize that intractable epilepsy in childhood has a different and more refractory profile compared to adults, owing to extratemporal epilepsies and developmental malformations.

1.148

NON-IDIOPATHIC FOCAL EPILEPSY IN CHILDREN: "CRYPTOGENIC" IS NOT IDENTICAL TO "PROBABLY SYMPTOMATIC"

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Rationale: The long-term prognosis for cryptogenic partial epilepsy in children remains poorly understood. We compared long-term outcome in a population-based group of children with cryptogenic vs symptomatic partial epilepsy diagnosed between 1980-2004.

Methods: Children (1 month through 17 years) who were newly diagnosed with non-idiopathic partial epilepsy between 1980-2004, while resident in Olmsted County, Minnesota were identified through the Rochester Epidemiology Database. Cases with idiopathic partial epilepsy syndromes were excluded. Medical records were reviewed to determine etiology, results of imaging and EEG studies, treatments used, and long-term outcome. Cases were defined as "cryptogenic" if they had a normal neurological exam, were developmentally normal, and had no lesion on neuroimaging, and as "symptomatic" if any of these features was not present.

Results: Of 356 children with epilepsy, 210 (59%) were non-idiopathic, localization-related. Of these, 203 (97%) were followed for >12 months (mean followup 159 months, SD 91 months). Seventy (34%) were cryptogenic. Symptomatic etiologies included prior brain insult (51), developmental delay alone (35), malformations of cortical development/tuberous sclerosis (21), mesial temporal sclerosis (7), vascular malformations (6), tumor (4), chromosomal abnormality (4), hypothalamic hamartoma (1) and dual pathology (4). Long-term outcome was significantly better in those with cryptogenic vs symptomatic etiology (intractable epilepsy at last follow-up - 4% vs 32%, $p<0.001$, seizure-freedom at last followup - 84% vs 61%, $p<0.002$, medication-freedom at last follow-up - 59% vs 33%, $p<0.002$). Epilepsy surgery was performed in 15% of symptomatic cases vs none of the cryptogenic cases.

Conclusions: One third of childhood non-idiopathic focal epilepsy is cryptogenic. This group has a significantly better outcome than those with a symptomatic etiology, and should be viewed as clinically distinct.

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NEONATAL EPILEPTIC ENCEPHALOPATHIES AND THEIR EVOLUTION TO HYPSARRHYTHMIA: ETIOLOGY AND ELECTROCLINICAL FINDINGS OVER TIME

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Rationale: West Syndrome is an age dependent epileptic encephalopathy characterized by infantile spasms, hypsarrhythmia and developmental delay. It is commonly seen in infants from 3 to 6 months. It can be preceded by neonatal seizures. We reviewed the EEGs of children with hypsarrhythmia to identify patients whose seizure onset was at or before the first month of life, the relationship between electrographic features and etiology, and the evolution of these findings over time.

Methods: Methods.

In a 8.5 year period, more than 15000 pediatric EEGs were recorded at UT Southwestern/Children's Medical Center, Dallas. On a database retrospective review we identified 95 patients with 1 or more hypsarrhythmic EEG's. 32 patients had a seizure onset at or before the first month of life (neonatal onset). Additional medical record review identified etiology and electroclinical findings.

Results: Of 95 children with hypsarrhythmia. 32 had a seizure onset at or before the first month of life. 17 were male and 15 female (ratio 0.8:1). Etiology was symptomatic in 29/32 (90.6%) vs 41/63 (65%) of children with a latter seizure onset ($p= 0.0072$). 18/32 (62%) children had hypoxic-ischemic encephalopathy, 5/32 (17%) had cortical dysplasia and 6/32 (20.6%) had other etiologies. There were 5 (16%) patients where hypsarrhythmia was first identified between 0-1 months, and 27 (84%) patients presented hypsarrhytmia after this age (2 to 84 months) . In EEG's were sleep was recorded, 50% of those with neonatal onset had some preserved normal architecture vs 65% of latter onset. 10/32 patients had an interictal EEG prior the diagnosis of hypsarrhythmia; of these 10/10 showed epileptform abnormalities. 9/32 patients had follow up EEG at least 6 months after hypsarrhythmia was identified. None of these was normal versus the latter onset group were 6/26 were normal. 22/32 of the patients had spasms only, 6/32 had spasms and other seizure type, 4/32 had other seizure types without spasms.

Conclusions: In our sample of children with hypsarrhythmia, the age of presentation was similar for children with neonatal seizures and those who have latter onset. Symptomatic etiologies were significantly more common among the neonatal seizure onset group. These children tended to have more severe disruption of background EEG (loss of all sleep architecture). None in the neonatal onset sample had a normal EEG at follow up or prior the hypsarrhythmic pattern was identified, compared to 23% of the children with a latter age of seizure onset who had normal follow up EEG's. In despite of the etiology, a seizure onset during the neonatal period in patients with hypsarrhythmia, may be associated to a more severe electroclinical outcome.

IMAGE: images/907167_A.jpg

(LEFT) Coronal FLAIR sequence MRI of the brain in an infant with left frontal cortical dysplasia. (RIGHT) Hypsarrhythmia pattern in the same patient. This child presented with neonatal onset seizures.

1.150

ICTAL NEOCORTICAL SLOW ACTIVITY AND IMPAIRED CONSCIOUSNESS IN TEMPORAL LOBE EPILEPSY

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Rationale: Partial seizures in temporal lobe epilepsy (TLE) are classified as complex-partial, resulting in a loss of consciousness, or simple-partial, associated with preserved consciousness. The mechanistic underpinnings of impaired consciousness in partial seizures are poorly understood. Investigators have previously suggested that unconsciousness during partial seizures may be related to bilateral temporal lobe involvement, seizure onset in the language-dominant hemisphere, or increased cortico-thalamic synchrony. Earlier work has indeed shown that temporal lobe seizures are often associated with bilateral slow rhythms and decreased cerebral blood flow in the frontoparietal neocortex. Ictal neocortical slow rhythms resemble cortical activity observed during sleep or deep anesthesia. However, no prior investigations have directly examined the relationship between ictal neocortical slow activity and behavioral unresponsiveness.

Methods: We analyzed intracranial electroencephalographic (EEG) recordings during 63 partial seizures in 26 TLE patients. Blinded reviewers analyzed behavioral responsiveness based on video recordings of seizures and classified consciousness as impaired (complex-partial) or unimpaired (simple-partial).

Results: We found significantly elevated delta-range 1-2 Hz slow activity in the frontal and parietal neocortices during complex-partial compared to simple-partial seizures. Also, fast beta-range EEG activity in the contralateral temporal lobe, indicating seizure propagation, was significantly correlated with slow delta activity in the frontoparietal neocortex. Furthermore, we observed that seizure onset in the language-dominant hemisphere and bilateral temporal lobe involvement were more common during complex- than simple-partial seizures.

Conclusions: We have proposed a 'network inhibition hypothesis' based on prior human and animal studies, in which subcortical arousal systems are disrupted by partial seizures, producing a depressed cortical state of slow activity and impaired consciousness. Our present findings illustrate that impaired consciousness is associated with ictal neocortical slow and bilateral temporal fast rhythms, raising the possibility that spread of seizure activity to bilateral temporal lobes may exert a powerful inhibitory effect on subcortical arousal networks. Further investigations are necessary to fully determine the role of cortical-subcortical networks in ictal neocortical dysfunction, and may ultimately lead to specific treatments targeted at preventing this negative consequence of TLE.

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VARIATION OF SEIZURE FREQUENCY BETWEEN ANOVULATORY AND OVULATORY CYCLES

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Rationale: Since 1) anovulatory cycles have higher estradiol/progesterone (E/P) ratios during the luteal phase than ovulatory cycles and 2) reproductive steroids have neuroactive properties such that estradiol may promote and progesterone may lessen seizures, we conducted an exploratory investigation to determine if seizure frequency differed between anovulatory and ovulatory cycles in women with intractable focal onset seizures. If so, we determined whether the difference was related to the midluteal serum E/P ratios.

Methods: 281 women, 13-48 years old, participated in the 3-month baseline phase of a prospective, multicenter investigation of adjunctive cyclic progesterone therapy for intractable focal onset seizures. The data come from the seizure-menses charts of 92 women who had both anovulatoy and ovulatory cycles during the baseline phase. Mid luteal progesterone levels e"5 ng/ml were used to designate cycles as ovulatory. Average daily seizure frequency (ADSF) for all seizures combined and each type of seizure considered separately (generalized tonic clonic seizures - GTCS, complex partial seizures - CPS, simple partial seizures - SPS) were compared between anovulatory and ovulatory cycles using paired t-tests. A relationship between the proportional differences in ADSF, i.e. anovulatory/ovulatory ADSF ratios, and the midluteal E/P levels, i.e. anovulatory/ovulatory E/P ratios, was determined using bivariate correlational testing.

Results: ADSF was 29.5% greater for GTCS during anovulatory than during ovulatory cycles (anovulatory: .237 ± .488 v ovulatory: .183 ± .440; t = 2.324, p = .028) (Table 1). ADSF did not differ significantly for CPS or SPS or for all seizures combined. The likelihood of finding a significant difference, i.e. power of the comparison, was .1068 for CPS and .0506 for SPS. Rates of anovulatory cycles were similar for GTCS (26.0%), CPS (28.8%) and SPS (26.3%) (÷2 = N.S.). Anovulatory/ovulatory GTCS ADSF ratios correlated significantly with anovulatory/ovulatory E/P ratios (Spearman rho = .663, p = .005).

Conclusions: Seizure frequency is significantly greater for GTCS, but not CPS or SPS, during anovulatory cycles than during ovulatory cycles. Since the increase in generalized seizure frequency during anovulatory cycles correlates with the proportional difference in mid luteal serum E/P level ratios between anovulatory and ovulatory cycles, these finding support a possible role for reproductive steroids in influencing the rates of seizure occurrence. Although seizure frequency is related to anovulation for GTCS only, the three seizure types (GTCS, CPS and SPS) do not differ in anovulatory rates.

Supported by NIH R01 NS39466

IMAGE: tables/889726_T1.jpg

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AURA ANALYSIS IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Rationale: We analyzed the distribution of different aura types in temporal lobe epilepsy (TLE) in relation to seizure origin (mesial versus extra-mesial; left versus right).

Methods: Video-EEG-documented seizures of 97 adult TLE patients were studied. Patients were were requested to describe their type of aura.

Results: a) In general, aura was significantly more frequent in mesial TLE, as compared to extra-mesial TLE; there was no statistically significant difference concerning lateralization. b) In the mesial group, we observed a homogeneous pattern of aura types, mainly represented by epigastric aura (55.6%), fear (20.4%), unspecific aura (14.9%), or

somatosensory aura (11.1%). In contrast, the extra-mesial group showed a very heterogeneous distribution of aura types. c) Noticeable distributions were observed for the following aura types: Epigastric aura occurred significantly more frequently in mesial TLE, when compared to extra-mesial TLE; however, without significant difference concerning lateralization. Olfactory aura and nausea occurred very rarely, but exclusively in mesial TLE. d) In some patients, two or three different aura types occurred during one seizure. In the mesial group, we found a homogeneous pattern: here, patients always reported either epigastric aura or fear, combined with other aura types. In the extra-mesial group, such a regular pattern was not observed. e) Finally, we analyzed the most frequent aura types epigastric aura, fear, unspecific aura, and somatosensory aura for the first semiological element occurring directly after the aura. Epigastric aura was mainly followed by restlessness, oral automatisms, or behavioural arrest, while the other aura types did not show a prefered distribution of first objective seizure elements.

Conclusions: In conclusion, the occurrence of aura, the type of aura, and the first objective seizure element occuring directly after aura may give useful information concerning differentiation of seizure onset in TLE.

1.153

WHICH SEMIOLOGY EXPLAINS AXIAL MUSCLE HYPOTONIA?

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Rationale: Inhibitory motor seizures have been classified including atonic seizure, astatic seizures, hypomotor seizures, akinetic seizures, negative myoclonic seizures and aphasic seizures. In contrast with the abrupt falls seen in patients with Lennox-Gastaut syndrome, the head drops in the patients showing axial muscle hypotonia during seizure were slow, taking 2-5 sec to fall down. Which special seizures cover axial muscle hypotonia as semiology?

Methods: We included 5 patients with inhibitory motor seizures. There were 2 males and 3 females. We excluded 1 male and 1 female who had aphasic seizures. A long-term video/electroencephalogram (EEG) monitoring, electromyogram (EMG), brain magnetic resonance imaging (MRI) and Single photon emission computed tomography (SPECT) were carried out and compared with previously reported cases.

Results: During video/EEG monitoring, patient 1 had 21 habitual seizures, patient 2 had none habitual seizures and patient 3 showed not inhibitory seizure, but bilateral asymmetric tonic seizure. Interictal EEG of Patient 1 showed C3, P3 sharp waves as interictal epileptiform discharges approximately once every 3~5 min during sleep. Ictal semiology consisted of abrupt onset of slow head drop or diminution of neck muscle tone. Consciousness is not impaired, and the neck muscle hypotonia returns to normal by degrees. In all of the seizures recorded by video, patient 1 fell down forward when they occurred while she sat down on the bed, and it took 20 to 30 sec to fall down forward. Ictal EEG started with low-voltage 15- to 18-Hz beta range activities in the vertex areas (Cz maximum), and then repetitive spikes were seen at the centroparietal to vertex area (F4, C4 to Cz), lasting 50-70 sec. (Fig. 1 A) EMG from the neck muscle revealed the neck muscle hypotonia and gradually restoring normal tone. (Fig. 1 B) MRI showed cortical dysplasia involving left parietal lobe. (Fig. 2 A) By using Statistical Parametric Mapping (SPM), the ictal blood flow increase in left parietal lobe. (Fig. 2 B)

Conclusions: Neck muscle hypotonia might be a feature of atonic seizures in partial epilepsy. Two possible mechanisms were implicated in atonic seizure development: (1) epileptic activities arising from the premotor areas directly inhibit primary motor cortex or are involved in voluntary movement integration and cannot function during 50-Hz electrical stimulation (negative motor area) or (2) sustained atonia with successive electromyogram (EMG) silent or hypotonic periods caused by epileptic discharges arising from the inhibitory area of the primary sensorimotor area.

IMAGE: images/906723_A.jpg

IMAGE: images/906723_B.jpg

1.154

CLINICAL SPECTRUM OF EPILEPTIC SPASMS IN CHILDREN

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Rationale: Epileptic spasms (ES) occur outside of West syndrome (WS) well-defined syndromes but have not been well characterized. The aim of this study is to compare etiologic, semiological, electrographic findings and other clinical features of ES in children with WS and children with ES who have never had WS (NoWS).

Methods: The video/EEG recordings of consecutive children evaluated in our EMU who were diagnosed as having ES were reviewed and information extracted in a standardized fashion.

Results: 102 children had WS from initial onset of epilepsy and at the time of the EMU visit, and 33 children had ES without any history of WS or other specific syndrome. Age at onset was younger in WS versus NoWS (5.5 mo vs 46.7 mo, $p<0.0001$). Distributions of underlying causes were similar in WS and NoWS (e.g. MCD 15% vs 12%, hypoxic insult 10% vs 12%, unknown cause 19% vs 15%, all $p>0.10$). Coexistence of other seizure types was more common in NoWS (39% vs 17%, $p=0.006$). Semiology differed with arms (91% vs 70%, $p=0.002$) and legs (72% vs 27%, $p<0.0001$) being involved more often in WS and head (70% vs 43%, $p=0.007$) involved more often in NoWS. Asymmetry was not significantly more common in WS than NoWS (32% vs 18%, $p=0.12$). The minimum frequency of clusters per day was similar in WS and NoWS (3.1 vs 3.2 $p=0.82$); however the minimum number of seizures per cluster was greater in WS (10.3 vs 4.6, $p<0.0001$). Seizures were more likely to be diurnal only in the NoWS group (27% vs 8%, $p=0.004$). Interictally, hypsarrythmia was present in 81% of WS and 12% of NoWS EEGs ($p<0.0001$). Generalized spike discharges were more common in NoWS (24% vs 10%, $p=0.03$) and discontinuous background was more common in WS (60% vs 36%, $p=0.02$). One or more normal background features were more commonly seen in NoWS than WS EEGs (76% vs 57%, $p=0.05$). Ictal findings did not differ significantly between the two groups.

Conclusions: There was a substantial proportion of children with ES who did not have WS or other recognizable syndromes. Ictal semiology and clustering varied between WS and NoWS as did certain interictal findings; however, underlying causes and ictal manifestations are similar. This raises questions concerning whether West is a discrete age-limited syndrome or whether differences in how WS vs NoWS manifest simply reflect age-related maturational differences in expression of the same underlying process.

1.155

ASPHYXIA AS A MECHANISM OF SUDDEN UNEXPECTED DEATH IN EPILEPSY

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Rationale: Sudden unexpected death in epilepsy (SUDEP) is the leading cause of mortality in patients with chronic uncontrolled epilepsy, and its etiologies are still largely unresolved. Here we report that a 35 year-old woman suffered SUDEP after having a generalized seizure in the prone position. The cause of her death was asphyxia from the convergence of post-ictal coma and positional airway obstruction and hypoventilation, rather than the commonly suspected peri-ictal cardiac arrhythmia or central apnea.

Methods: A 35-year-old woman with medically intractable complex partial epilepsy admitted for inpatient long-term video-EEG monitoring as part of a pre-surgical evaluation. She was taking oxycarbazepine 2400mg and topiramate 200mg daily that were gradually withdrawn. In the early morning of hospital day four, she was found unresponsive in bed. Immediate attempts at cardiopulmonary resuscitation and cardioversion were unsuccessful.

Results: Review of video-EEG recordings revealed that she was sleeping in the prone position with her face partially in a pillow before her seizure. While she was in her sleep, a partial seizure began in her right temporal lobe and subsequently evolved into a secondarily generalized tonic-clonic seizure. The seizure lasted approximately two minutes. Postictally, her EEG background was initially suppressed in amplitude. Two minutes after the seizure, it flattened further and demonstrated only prominent ECG artifacts for the remaining course of SUDEP.

ECG showed a sinus tachycardia with a HR 120/min immediately after the seizure. The heart rate gradually slowed to 68/min with wide QRS complexes. Asystole began two minute after the seizure and lasted for approximately one minute. Surprisingly, the ECG activity reappeared with a slow HR of 30-50/min and lasted for almost 10 min.

Respiratory body movements were clearly observed on the video immediately after the seizure. Rhythmic muscle artifacts on EEG were synchronized with respiratory movements. Postictally she was tachypneic with a respiratory rate at ~30/min initially. These soon increased to ~45/min for two minutes along with greater respiratory efforts. The patient subsequently became apneic for one minute. However, respiratory effort then reappeared along with ECG activity. Irregular and slow gasping respiratory efforts between 5-15/min lasted for almost 10 min. Arrest of all respiratory efforts occurred at approximately the same time as cardiac arrest 13 min after the seizure.

Conclusions: The presence of enduring cardiac activity and respiratory effort for the first two minutes after the seizure suggests that neither peri-ictal cardiac arrhythmia nor central apnea was the likely mechanism of the SUDEP. Postictally,the presence of respiratory effort at an increased rate and intensity strongly suggests that asphyxia secondary to airway obstruction and hypoventilation was the main cause of death. SUDEP may share the similar etiology to sudden infant death syndrome (SIDS) and is likely preventable.

IMAGE: images/890867_A.jpg

Fig 1: Scalp EEG displayed in a common average referential montage using international 10-20 plus sub-temporal supplemental electrodes (F9, T9, M1, F10, T10, and M2). A: Pre-ictal EEG: the patient was awakening from sleep with a return of alpha rhythm. ECG showed regular heart rate of 60/min. B: Focal ictal onset from the right temporal region (electrodes F8, T8 and M2). ECG showed an ictal sinus tachycardia with heart rate of 120/min. C: Generalized tonic ictus: Both EEG and ECG were obscured by muscle artifacts.

IMAGE: images/890867_B.jpg

Fig 2: Postictal EEG at10μV/mm. A: Seizure terminated after the final clonic jerking. Postictal EEG was slow and markedly attenuated and superimposed with respiration- related muscle artifacts (RR 30/min) which were synchronized with respiratory movement on the video. Electrode artifacts on F4 and C4 electrodes. ECG showed sinus tachycardia with HR 120/min. B: Postictal EEG was recorded 1 min after seizure termination and showed persistent suppression and increased respiratory rate and effort with more prominent muscle artifact on EEG. ECG showed wide QRS complex with HR 68/min. C: Postictal EEG recorded 2 min after the seizure termination showing the onset of apnea and asystole.

1.156

CLINICAL SIGNIFICANCE OF SCN1A GENE MUTATIONS - PARENT, PHYSICIAN AND GENETIC PERSPECTIVES

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Rationale: Most mutations in the SCN1A gene associated with epilepsy are novel and how they relate to the phenotype and quality of life of that individual and whether genetic knowledge will alter management is uncertain. We characterised SCN1A mutations based on mutation class and physico-chemical properties and related this to clinical symptoms and parent rated severity of epilepsy and quality of life measures. Parent and physicians experiences of genetic testing were assessed to ascertain if testing resulted in management change.

Methods: We reviewed clinical referral and genetic data on 268 individuals with SCN1A mutations identified in our centre. Mutations were classified as mild/moderate if they were missense with a physico-chemical property difference in amino acids (Grantham score - GS) d" 100, and severe if they were truncating or missense with GS > 100. Parents and physicians completed questionnaires on the role of genetic testing. Parents completed the Paediatric Quality of Life Inventory, Impact of Paediatric Epilepsy Scale, and Epilepsy and Learning Disabilities Quality of Life Questionnaire.

Results: 94 individuals (35%) had a mild/moderate SCN1A mutation and 174 individuals (65%) a severe mutation. In comparison to a mild/moderate mutation, a severe mutation was associated with earlier disease onset (6 vs 8 months; $p < 0.001$), more frequent myoclonic seizures (71% vs 57%; $X^2 = 5.0$; $df = 1$; $p = 0.025$), more frequent acquired movement disorder (47% vs 28%; $X^2 = 6.5$; $df = 1$; $p = 0.010$) and worse developmental outcome ($X^2 = 13.1$; $df = 4$; $p = 0.011$). 135 parents and 101 physicians of mutation positive patients returned postal questionnaires. Severe mutations were associated with overall poorer rated quality of life ($p = 0.007$), more severely rated epilepsy ($p = 0.001$), worse rated language ability ($p = 0.020$), worse rated school and learning performance (0.039) and lower health related quality of life

for physical (p = 0.030) and daily tasks (p = 0.014). In 117/135 of cases (87%) parents reported genetic testing was helpful. In 73/135 (54%) it led to a change in treatment (80% introduction of new medication, 20% stopping medication). Treatment change improved seizure control in 55% and reportedly had a positive effect on development in 27%. In 45/101 of cases physicians reported that genetic testing allowed them to make an earlier diagnosis than on clinical criteria alone. In 47% of cases it helped prevent misdiagnosis and in 70% the child was saved additional investigations. Genetic data influenced choice of medication in 72% of cases and changes consequent upon testing resulted in improved seizure control in 33%.

Conclusions: SCN1A genetic testing can result in management changes in children with epilepsy. Truncating mutations and missense mutations with a high Grantham score are more likely to be associated with a poorer quality of life, poorer cognitive abilities and worse seizure control. Parents and physicians have similar perspectives on the role of SCN1A testing.

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A NOVEL GENETIC OCCIPITAL EPILEPSY SYNDROME IN SIBLINGS SHOWING CLINICAL AND EEG-FMRI CONCORDANCE

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Rationale: The benign occipital epilepsies of childhood include Panayiotopoulos Syndrome and Gastaut syndrome; a third syndrome, Idiopathic photosensitive occipital epilepsy may also begin in childhood. These syndromes are defined according to age of onset, seizure semiology and EEG features including photosensitivity. We describe siblings with a novel occipital epilepsy syndrome and localize their interictal epileptiform activity using EEG with functional MRI (EEG-fMRI).

Methods: A sister and brother presenting with refractory occipital seizures were identified and detailed electroclinical information obtained. Functional imaging was performed at 3 Tesla with EEG recorded during continuous acquisition of gradient-recalled echoplanar images. In-scanner EEG was reviewed off-line, all interictal epileptiform discharges were marked as events of interest, and an event related analysis using SPM8 was performed.

Results: Seizure began at 12 years in the girl and 10 years in her brother. Seizure semiology involved elementary visual phenomena or visual loss. In longer seizures, head and eye deviation to the right was noted in the girl and to the left in the boy. At times, loss of awareness and post-ictal headache was seen in the girl. The boy often experienced headache while awareness was preserved. Neither sibling experienced autonomic symptoms. The boy has had a single seizure with fever at age 2 but other seizure types were not seen. They developed frequent refractory seizures (10 or more daily) despite multiple anti-epileptic drugs. The ketogenic diet substantially reduced seizure frequency in the 17 year old sister and has recently been commenced in her 11 year old brother. They were the only children to unrelated parents with no family history.

EEGs demonstrated a normal posterior dominant rhythm with episodic occipital slowing. Occipital fast activity and sharp and slow discharges occurred bilaterally, with left-sided predominance in the boy. Seizures were recorded in both and confirmed a localized occipital onset. There was no fixation-off sensitivity. Structural imaging was normal. Siblings had normal intellect without regression. Celiac serology, mitochondrial and POLG mutation screening were negative.

Both subjects demonstrated BOLD signal change in the occipital cortex during fMRI. The sister showed bilateral negative BOLD in the lingual gyrus while her brother showed positive BOLD change in the left middle occipital gyrus. There was positive BOLD signal change in the cerebellum, bilaterally in the girl and left lateralized in the boy. The girl also demonstrated bilateral anterior thalamic positive BOLD.

Conclusions: This novel childhood onset genetic occipital epilepsy syndrome is characterized by frequent, brief, refractory occipital seizures with onset at around 10 years of age. Functional imaging suggests a network involving occipital and cerebellar circuits is important for seizure generation. The striking electro-clinical concordance in siblings provides strong evidence for a genetic basis, but it is unclear if the etiology is monogenic or polygenic.

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AMYTAL VERSUS BREVITAL:DIFFERENCES IN WADA TEST PERFORMANCE IN TEMPORAL LOBE EPILEPSY PATIENTS GILLEN, R.W., RITACCIO, A.L. LYNCH, T., & BARBA A.L. NEUROLOGY, ALBANY MEDICAL CENTER, ALBANY, NY, USA, SUNNYVIEW REHABILITATION HOSPITAL, SCHENECTADY, NY, USA

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Rationale: A shortage of Amytal necessitated use of other agents for Wada testing. While a commonly used alternative is Brevital,there is concern that it does not detect memory asymmetries as well as Amytal,and may be a poor predictor of postsurgical memory change(Andelman et al,2006. The current study evaluated the relative effectivenesss of Brevital and Amytal in detecting memory asymmetries in temporal lobe surgery candidates.

Methods: 24 left(LTLE)and 26 right(RTLE)candidates for temporal lobe resection underwent Wada testing as part of the pre-surgical evaluation. 24 patients were given Amytal (average dose = 107 mg),while 26 received Brevital(average dose = 5 mg). Wada testing involved use of the Medical College of Georgia protocol with recognition memory(number of objects correctly identified minus 1/2 the number of false positive responses) as the critical measure. Comparisons included: 1)recognition scores by side of injection and 2)a memory asymmetry score derived by subtracting recognition scores from injection of the non-compromised TL from scores of the injected compromised TL. Higher scores reflected greater memory asymmetry.

Results: While memory asymmetry scores tended to be higher with Amytal(2.98,sd = 3.1)as opposed to Brevital(1.46, sd = 3.0)injections, this difference did not achieve statistical significance($t = 1.86$ $p < .077$, $df = 48$). Results of recognition scores for RTLE/LTLE by side of injection for Amytal are presented in Table 1, with Brevital results in Table 2. With Amytal injection, differences were found between RTLE and LFTE patients with both right-sided ($t = -2.1$ $p < .048$, $df = 21$)and left-sided (($t = 3.18$ $p < .005$, $df = 20$) injections. With Brevital injections,

differences did not achieve significance for either right(t = -1.44,p< .163, df = 23)or left-sided injections(t = 1.97, p< .06, df = 23).

Conclusions: Memory asymmetry scores tended to be higher following Amytal versus Brevital injections, though the differences did not achieve significance. Differences were found between drugs when comparing side of injection with seizure focus. It would be expected that injection of the epileptogenic TL would result in less memory impairment than injection of the non-involved side. With Amytal, the expected discrepancies were found between hemispheric focus and side of injection in both right and left TLE. With Brevital, the discrepancies did not achieve significance for either right or left-sided injections. The current study is limited by a small sample size. While patients were not randomly assigned and could differ in critical ways, significant differences were not found between the groups on either demographic or epilepsy related variables. The current study provides further evidence that Amytal and Brevital may not be interchangeable in terms of determining integrity of memory functioning.

Table 1:Amytal: Recognition Scores by Side of Injection in Right & Left TLE

IMAGE: tables/889749_T1.jpg

Table 2 Brevital: T Tests for Recognition Scores by Side of Injection in Right & Left TLE

IMAGE: tables/889749_T2.jpg

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SECONDARILY GENERALIZED CLONIC-TONIC-CLONIC SEIZURE WITH RETAINED CONSCIOUSNESS

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Rationale: Assessment of consciousness is integral to characterization of epileptic seizures. Generalized seizures have more than minimal involvement of bilateral hemispheres, are associated with unresponsiveness and lack of ictal subjective experience. We report a patient with prolonged secondarily generalized clonic-tonic-clonic seizure with retained consciousness.

Methods: Continuous electrocardiography and video electroencephalography (EEG) were performed.

Results: 58-year-old right-handed woman status-post partial resection of left parasagittal parietal meningioma (Fig. 1) presented with recurrent spells of mumbling speech, full body jerking, and maintained awareness and recall. Video EEG captured one 22 minutes, 6 seconds seizure (Fig. 2). EEG onset began 1 second prior to clinical onset with rhythmic 1 Hertz (Hz) sharp waves over left centroparietal region (P3, Pz) evolving to rhythmic 3.5 Hz sharp waves spreading to Fz, Cz. At clinical onset she had right hand, arm clonic activity progressing to superimposed tonic right arm flexion and facial posturing within 2 seconds, during which she answered complex questions appropriately, read and demonstrated good immediate and recent recall. As ictal pattern spread diffusely to both hemispheres (max P3, Pz) left arm tonic posture developed and she still conversed. Ictal pattern evolved to diffuse bilateral rhythmic spikes (max P3, Pz) associated with forceful tongue protrusion and generalized tonic-clonic activity, figure of four posturing. With continued generalized polyspike waves, tongue retracted, generalized tonic-clonic activity continued, and she followed commands including looking at the nurse and partially reading the sign until she became unresponsive at 5 minutes. Spontaneous clinical offset was 20:01 and EEG offset was 22:06.

Conclusions: Our patient had seizures symptomatic of parasagittal meningioma. Parasagittal meningiomas present with seizures at a frequency of 27-62%, usually generalized. Surgery cured epilepsy in 62.7% of all meningiomas, but pre- and postoperative prevalence of epilepsy was unchanged in parasagittal meningiomas. Our case is unusual due to elements of retained consciousness demonstrated by following commands and reading during clinical and electrographic secondarily generalized seizure activity. There are few reported cases of generalized seizures with retained consciousness. Common to all is onset near sensorimotor cortex, right hemisphere (4 of 5), and 90 seconds duration. This contrasts to our patient with left sided onset and prolonged seizure that spontaneously resolved. During her generalized seizure, brain regions determining level and content of consciousness were relatively spared. After five minutes, ictal pattern likely spread to portions of subcortical structures, limbic region and/or frontoparietal association cortices associated with loss of awareness. Our patient was diagnosed with focal epilepsy characterized by simple and complex focal seizures that may secondarily generalize with clonic-tonic-clonic activity and retained consciousness.

IMAGE: images/904467_A.jpg

MR imaging of the brain: Evidence of prior left craniotomy with encephalomalacia and postoperative changes in the left posterior frontal and parietal lobes with surrounding gliosis. Residual or recurrent homogeneously enhancing mass is noted in the left parasagittal region with invasion or effacement of the superior sagittal sinus. Left top panel: Axial T1. Left bottom panel: Axial T2. Right top panel: Sagittal T1 with contrast. Right bottom panel: Coronal T1 with contrast.

IMAGE: images/904467_B.jpg

Portions of Seizure EEG Tracing: Settings: Bipolar anterior to posterior montage, Sweep speed: 30 mm/sec, Sensitivity: 7.5 µV/mm, High-frequency filter: 70 Hz, Low-frequency filter: 1 Hz.

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MIDBRAIN-HINDBRAIN MALFORMATIONS IN PATIENTS WITH CORTICAL MALFORMATIONS

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Rationale: : Midbrain and hindbrain represent posterior fossa structures which comprise cerebellum, brainstem and related cerebrospinal fluid spaces. Developmental disorders affecting midbrain-hindbrain have been increasingly recognised during past two decades due to advances in neuroimaging. Midbrain-hindbrain malformations may occur as isolated abnormalities or as part of larger developmental disorders, yet large cohort data on their association with supratentorial cortical malformations, defining the clinical and imaging spectrum is

lacking. The aims of this study were to investigate the spectrum of midbrain-hindbrain malformations in patients with supratentorial cortical malformations and epilepsy and to compare the clinical and imaging features of two groups of patients: those with supratentorial cortical malformations and midbrain-hindbrain malformations to those with supratentorial cortical malformations and without midbrain-hindbrain malformations.

Methods: Two hundred and twenty patients (116 women, mean age 31±16.6, range 2-76) with supratentorial cortical malformations and epilepsy were identified at the Departments of Neurology and Pediatrics, Innsbruck Medical University, Austria. All underwent highresolution MRI (1.5-Tesla) between 2002 and 2008. Midbrain-hindbrain structures were visually assessed by three independent raters.

Results: Midbrain-hindbrain malformations were seen in 17 %, 38/220 of patients (the most common was Dandy-Walker malformation - 32%, 12/38). Unilateral brainstem hypoplasia (21%, 8/38) was invariably associated with ipsilateral perisylvian polymicrogyria. No other significant associations between different midbrain-hindbrain malformations and supratentorial cortical malformations were observed. Patients with midbrain-hindbrain malformations had a higher rate of extensive bilateral supratentorial cortical malformations (63%, 24/38 vs. 36%, 66/182; p=0.004), dysgenesis of corpus callosum (26%, 10/38 vs. 4%, 7/182; p<0.001), hippocampal abnormalities (52%, 20/38 vs. 27%, 49/182; p=0.004), learning disability (71%, 27/38 vs. 38%, 70/182; p<0.001), delayed developmental milestones (68%, 26/38 vs. 35%, 63/182; p<0.001), as well as earlier age at seizure onset (mean 7.6 years vs. 9.5 years; p=0.043), compared to those without midbrain-hindbrain malformations

Conclusions: The presence of midbrain-hindbrain malformations in patients with supratentorial cortical malformations could be an indicator of a global cerebral developmental disorder. This study expands our understanding of the spectrum of imaging and clinical features of midbrain-hindbrain malformations in patients with supratentorial cortical malformations and epilepsy

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PROSPECTIVE ANALYSIS OF SEIZURE FREQUENCY IN ESTABLISHED EPILEPSY

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Rationale: Although the incidence of seizure (SZ) freedom has been studied in a few syndromes with a good prognosis, such as benign Rolandic epilepsy and childhood absence epilepsy, it has not been studied in most epilepsy syndromes. The frequency of SZs among those who continue to have SZs has not been prospectively studied. We prospectively collected data over a long duration to determine the SZ frequency distribution and SZ freedom rate in established epilepsy patients with well classified SZ types and epilepsy syndromes.

Methods: Standardized data were prospectively collected by epileptologists from patients seen in the UVA Epilepsy Clinic from April 1998 to November 2004. Data was acquired directly from patients and medical records. Analysis was limited to patients with definite epilepsy at least 5 years old. SZ frequency (number per month) was collected at each visit for each SZ type. The most recent SZ frequency collected is considered the "current SZ frequency". A historical maximum monthly frequency and minimum monthly frequency was also collected, as well as demographics, ILAE SZ type, ILAE epilepsy syndrome, etiology, EEG results, neuroimaging, family history, and current and prior antiepileptic drug use.

Results: A total of 1639 patients were analyzed. Overall, mean current age was 31.9 years, mean age at SZ onset was 14.4, and 49% were female. Overall, 60% (976 patients) had only partial onset SZ, 37% (602 patients) had only primary generalized SZ and 2% (61 patients) had mixed partial and generalized SZ. Median current SZ frequency was lower in partial SZ (2.6/mo) compared to primary generalized (5.0/mo) and mixed (9.0/mo). Maximum SZ frequency was lower in partial (32/mo) than primary generalized (46/mo) and lower yet in mixed (24/mo). Rate of SZ freedom was lower in partial (49%) than primary generalized (62%) and similar to mixed (42%). Differences between partial and generalized were significant (p< 0.001). Analysis of each individual SZ type was determined. For primary generalized tonic-clonic SZ (GTC) the current median SZ frequency was 5.0/mo, maximum SZ frequency 13.0/mo, and SZ freedom rate 77%. Absence SZ had a higher current SZ frequency (9.0/mo) and maximum SZ frequency (220/mo) and a similar rate of SZ freedom (70%). Complex partial SZ had a lower current SZ frequency (2.5/mo) and maximum SZ frequency (37/mo) and lower rate of SZ freedom (48%). Secondary GTC SZ had the lowest current SZ frequency (1.0/mo) and maximum SZ frequency (9.1/mo) and highest rate of SZ freedom (78%). Among epilepsy syndromes, SZ freedom was most likely in childhood absence (70%), least likely in Lennox-Gastaut (25%), and intermediate in mesial temporal lobe epilepsy (45.4%).

Conclusions: Knowing the specific rates of SZ freedom and SZ fequency has broad implications for understanding epilepsy. These data are of significant importance for understanding expected outcomes from treatment, what constitutes refractory epilepsy, whether patients in clinical trials are representative of other epilepsy patients, and the natural history of treated epilepsy.

1.162

CLINICAL SIGNIFICANCE OF PHOTOSENSITIVITY IN EARLY CHILDHOOD EPILEPSY

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Rationale: In the classification of photoparoxysmal response (PPR), only type 4 (generalized spikes and wave or polyspike wave) is thought to be of clinical significance. More specifically, a PPR type 4 in the very young has been reported to be pathognomonic of certain aetiologies.

Study aims at evaluating the clinical significance of PPR in children <5 years of age.

Methods: Retrospective review of case notes and EEG characteristics of patients under the age of 5 years with a history of seizures who demonstrated type 4 PPR following intermittent photic stimulation during routine EEG performed between 2003-2010 .

Results: Type 4 PPR was demonstrated in 41/6627 (0.6%) children (19 girls) less than 5 years.

Age at the onset of epilepsy (0.3 to 56 months, mean: 22.6 m) was categorised into two groups: (A) 0-24 m and (B) 25-60 m.

In Group A (n=25, mean age onset 9.4m) 6 (24%) had a definitive syndrome diagnosis (SMEI/Dravet's syndrome). Of the 19 with no syndrome diagnosis, 18 were associated with generalised seizures and one with focal seizures.

In group B (n=16, mean age onset 44m), 10 (62.5%) had a distinct epilepsy syndrome diagnosis of which 5 (50%) had childhood absence epilepsy (CAE), 3 myoclonic absence, 1 myoclonic atonic and 1 Lennox Gastaut Syndrome.

A history of status epilepticus (11/41; 27%) was found only in Group A ,(11/25; 45.8%).

There was an associated clinical correlate with PPR in 33/41 (80%).

Conclusions: In children presenting with epilepsy < 24m, early PPR is confirmed as a feature of SMEI, but there are few other currently recognised syndrome associations. However, there is a strong association with status epilepticus.

With older onset of presentation, a recognised syndrome diagnosis is more likely.

The significance of PPR<24m requires further evaluation.

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IDIOPATHIC HEMICONVULSION-HEMIPLEGIA SYNDROME (HH): MRI FOLLOW-UP FINDINGS IN 6 PATIENTS

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Rationale: Hemiconvulsion-hemiplegia (HH) syndrome is characterized by the occurrence of prolonged unilateral convulsions during the course of a febrile illness in children less than 4 years of age, followed by ipsilateral, transient or definitive, hemiplegia. Later, focal epilepsy is often observed (Gastaut H., 1960). HH syndrome can be idiopathic or symptomatic; the former being provoked during non-specific febrile episode and the latter emerging in cases with underlying brain pathology (Sakakibara T., 2009). Although the clinical features and natural history of HH syndrome have been well described (Gastaut H., 1960), the differential diagnosis of HH in the acute phase is a challenge requiring exclusion of infective, vascular and metabolic aetiologies. A few neuroradiological longitudinal studies were reported with a peculiar aspect of unilateral brain oedema at the time of the initial status epilepticus (SE), followed by global cerebral hemiatrophy independent of any vascular territory (Sankhyan N., 2008).

Methods: We report longitudinal neuroimaging data of 6 patients presenting idiopathic HH syndrome.

Results: All 6 patients presented during a febrile illness hemiclonic status epilepticus leading in 4 patients to persistent hemiplegia and to transitory deficit in 2. Median age at last observation was 6.5 years (range: 2.2-15 years). Follow-up ranged from 1 to 13 years.

Early MRI (1-10 days from the SE) showed in all a hemispheric cytotoxic oedema. T2 and FLAIR hyperintensities were observed in temporal, parietal and occipital areas in 3 patients, in caudate and thalamus nuclei in 2 and in hippocampus in one.

In intermediate stage (11 days- 1 month), the reduction of signal intensity abnormalities and of ADC values were consistent with a reduction of cytotoxic oedema.

During late stage (> 6 months), a selective cortical-subcortical atrophy of the affected hemisphere was documented in all, affecting thalamus and caudate nuclei in 2 patients and hippocampus in one. Temporal and occipital gliotic areas were observed in 2 patients.

Conclusions: This is the largest series of patients presenting idiopathic HH with longitudinal MRI follow-up including diffusion sequences. Our MRI findings showed a hemispheric cytotoxic reversible oedema involving mostly temporal and posterior cerebral regions and followed by a cortical-subcortical atrophy. We discuss the role of a selective brain vulnerability to an inflammatory-mediated insult in the determinism of HH. From a developmental point of view, an age-depending selective brain vulnerability could act as a modulator on the effects and the extension of inflammatory mechanisms and might explain a large spectrum of "immune mediated" epilepsies. Caudate and thalamus involvement, not previously reported, suggests a mainly functional and/or metabolic phenomenon.

1.164

INVESTIGATION OF FIVE CASES WITH EATING EPILEPSY

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Rationale: Reflex epilepsy syndromes are important clues for investigating complex mechanisms of epileptogenesis. We present the clinical and EEG characteristics of five eating epilepsy cases, which is a very rare form of reflex epilepsy.

Methods: Four males and one female patient (0.0005% of all patients) aged between 25-62 years, had therapy resistant simple partial, complex partial and secondarily generalized seizures triggered with eating besides spontaneous seizures.

Results: Their ages at onset were between 10-51 years and all had an initial precipitating event (such as head or birth trauma and neonatal convulsions); interestingly. The seizures mostly associated with having dinner in three patients; but they occurred at the breakfast too, in 2 patients. In 4 neurologically normal patients, the seizures were induced with a longer latency such as in the middle of the meal or even closely after the end, whereas in the last male case with mental retardation and right hemiparesis, the seizures were triggered by swallowing and at the beginning of the meal suggesting two different mechanisms. Three patients had normal MRI's, whereas one had sequel lesions involving the left parieto-occipital regions and one had meningioma involving the left frontal extra axial region. The interictal EEG's showed frequent spikes and slowing over a large area on the left temporal region in 4 and over right temporal area in one of them. The EEG focus persisted for more than 20 years despite extensive anti-epileptic drug treatments in one case. We are able to record eating related seizures originating from the left anterior temporal region in two cases. PET investigations are concordant with the EEG foci in 2 cases.

Conclusions: Our study showed that eating epilepsy is extremely rare and occurred usually after a silent period in patients who had an initial precipitating event for epilepsy. The seizures originated from the left temporal region mostly and triggered by dinner or breakfast with a long latency in most of the cases.

1.165

BENIGN TEMPORAL LOBE EPLIEPSY: A CASE SERIES

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Rationale: Temporal Lobe Epilepsy (TLE) is commonly perceived as being drug resisant in nature. Recently, attention has been drawn to "benign" variants of TLE: epilepsy that is well controlled for long periods on a low dose of one anti-epileptic medication. The aim of this study was to describe our experience with this entity.

Methods: The charts of patients presenting to our Epliepsy Centre were reviewed and patients meeting the following criteria were evaluated: a diagnosis (clinical, radiological or electrographic) of temporal lobe epilepsy that has been well controlled (less than one seizure per month) for a period of greater than two years using only one or no anti-epileptic medications.

Results: Ten patients were reviewed in total. Eight out of ten patients were female. Mean age was 53.9 years (S.D. = 21.3). The mean age of seizure onset was 32 years (S.D. = 19.0). All patients suffered from complex partial seizures and 50% had radiographical evidence of mesial temporal lobe sclerosis.

Conclusions: This case series illustrates that TLE includes a benign variant that is well controlled on one anti-eplieptic medication despite the presence of mesial temporal lobe sclerosis in most cases. Recognition of this syndrome is crucial in further surgical evaluation of patients presenting with TLE, especially in the context of mesial temporal lobe sclerosis.

1.166

REFLEX SEIZURES: CLINICAL AND NEUROPHYSIOLOGICAL FEATURES

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Rationale: Reflex seizures are provoked by a specific stimulus and have been divided into pure reflex epilepsies and reflex seizures also associated with spontaneous seizures. The latter group typically has symptomatic epilepsy. The mechanism of reflex seizures has been reported to be dependent on cortical hyperexcitability. However, there is evidence from animal studies that stimulus provokable seizures arise from the brainstem and occur because of insufficient cortical inhibition. Detailed clinical and neurophysiological features of 11 children with reflex seizures are presented, providing evidence to support the hypothesis that reflex seizures arise in the brainstem and result from insufficient cortical inhibition.

Methods: 11 children with stimulus-sensitive seizures were studied in detail. V-EEG monitoring results were included in the analysis. Review of the literature on animal models of reflex seizures with an emphasis on available information as to seizure mechanism was considered in interpreting the data.

Results: See Table 1.

Conclusions: 11 children with acquired startle or other reflex seizures are presented. Reflex seizures likely result from a lack of cortical modulation on subcortical pathways involving the reticulo-thalamic circuitry. Infantile spasms, other age-dependent epileptic encephalopathies, and neonatal seizures are thought to involve the brainstem, with some of the seizures termed "brainstem release phenomena". Startle seizures typically involve patients with early life extensive cerebral damage. The generalized nature of startle seizures despite a variety of cortical substrates suggests a brainstem origin and propogation via subcortical networks to the cortex or spinal cord.

The startle reflex is a motor response originating in the lower brainstem. Startle seizures may require the proprioceptive input of the startle via the lemniscal pathway to the sensorimotor cortex. Although Chauvel et al.(1992) demonstrated a cortical origin (motor and premotor cortex) in 20 patients with stimulus-provoked seizures, it seems more likely that cortical activation follows the activation of subcortical networks and that there is a lack of inhibition or "gating" of the stimulus. Subcortical networks have been proposed to explain seizures in hydranencephalic patients.

Animal models of stimulus-sensitive seizures have demonstrated a mesencephalic origin; in some models there is no (cortical) EEG correlate, particularly if the origin of the seizures is lower brainstem. Interestingly, in our most severely affected patients there was no EEG correlate seen as well.

Patient #1 is of great interest in that he had a global deficiency of neurotransmitters on analysis of CSF. In one animal model (the genetically epilepsy prone rat—GEPR), serotonin system abnormalities have been described in the superior collicus and treatment with an SSRI ameliorated the seizures. With additional study of these patients, who are typically refractory to conventional AED therapy, there may be novel treatment approaches based on increased understanding of the neurochemistry of subcortical, brainstem systems.

Neurological Profile in Reflex Seizures

IMAGE: tables/906175_T1.jpg

ACC=agenesis of the corpus callosum, CC=corpus callosotomy, RE=refractory epilepsy, SGDD=severe global developmental delay, LD=leukodystrophy, GTC=generalized tonic clonic, CPS=complex partial seizure, GPSS=generalized polyspike and slow wave, ESES=electrical status of sleep, SCT=stem cell transplant

1.167

SAME NAME - DIFFERENT STORY: HETEROGENEITY IS TYPICAL FOR RASMUSSENS ENCEPHALITIS - AN EVALUATION OF 34 CASES

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Rationale: Since the first description of Rasmussens encephalitis (RE) several anecdotal reports and small case series have been published addressing the rare epilepsy syndrome characterized by unilateral, progressive hemispheric inflammation of unknown etiology. Larger

series are lacking and insights into consistent patterns of disease activity and phenomenology are missing.

Methods: A chart review of 34 RE patients (range 1.8 - 14.7 years at first seizure) from the Bethel Epilepsy Centre, Germany (1988-2006) was systematically performed focusing on initial presentation, clinical course, EEG changes, neuroimaging findings and long-term outcome. Diagnosis of RE was based on European guidelines (Bien et al., Brain 2005, 128, 460).

Results: Despite few consistent observations (26 out of 34 patients developed epilepsia partialis continua [EPC], 31 out of 34 hemiparesis [HP], initial status epilepticus implied bad prognosis), heterogeneity and unpredictability were the main characteristic features of RE.

1)Onset was highly variable and could be acute and severe, slow and mild, or slow and severe.

2)Severity and frequency of EPC correlated poorly with degree of HP.

3)Prodromal, acute and residual phases could be diagnosed in 90%, but showed interindividually significant variations with regard to length, intensity and transition to the next stage.

4)Imaging findings (most frequently temporal T2 signal increase on MRI) and EEG results developed in highly variable time lines and had poor correlation to the clinical course.

5)Long-term outcome was unpredictable: the spectrum ranged from acute onset with major imaging findings and good outcome to mild onset, few changes on imaging and severe disability.

Conclusions: This large series of RE patients suggests that heterogeneity is a key finding in Rasmussens encephalitis and predicting long-term outcome is impossible in an early stage. Our understanding of the way “disease markers” in RE intercorrelate and determine overall prognosis is poor. The underlying pathophysiological processes resulting in various phenotypes are speculative.

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CLINICAL AND IMMUNOLOGICAL MARKERS IN STEROID RESPONSIVE ENCEPHALOPATHY ASSOCIATED WITH AUTOIMMUNE THYROIDITIS

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Rationale: Steroid Responsive Encephalopathy Associated with Autoimmune Thyroiditis (SREAT) is a rare and poorly understood neurological condition. Patients present with elevated serum levels of anti-thyroid peroxidase (anti-TPO) antibodies and intractable adult-onset epilepsy. These patients may benefit from steroid treatment.

Methods: Seven patients in Comprehensive Epilepsy Clinic at London Health Sciences Centre were identified as having both elevated anti-TPO antibodies and medically intractable adult onset epilepsy. They were worked up and matched with seven controls with medically intractable adult onset epilepsy but no evidence of elevated anti-TPO antibodies.

Results: Each group consisted of 5 females and 2 males. Average age in the anti-TPO group was 38± years versus 34± years in the control group with average age of onset being 33±years in the anti-TPO group versus 28± years for the controls. The patients in both groups were on an average taking 2 anti-eplieptic drugs (AEDs). Five of the anti-TPO patients suffered from other auto-immune conditions versus only one of the controls ($p<0.05$). Average serum Anti-TPO levels were 240± u/L in the anti-TPO group versus 13± u/L in the control group. Average serum Anti-Thyroglobulin levels were 1599± u/L in the anti-TPO group versus 144± u/L in the controls. Finally, average Thyroid Stimulating Hormone (TSH) levels in the anti-TPO group were 2.68± u/L versus 2.7± u/L in the control group. Steroid therapy was initiated in one of the patients from the anti-TPO group which resulted in a significant reduction in the number of her seizures.

Conclusions: Of the seven patients described here with elevated anti-TPO antibodies, one was offered a trial of steroid therapy and witnessed a significant reduction in seizure frequency as a result. This study highlights the benefit of investigating for a potential autoimmune pathology in cases of intractable adult onset epilepsy as treatment with steroids may prove to be both safe and efficacious. Clinical suspicion for SREAT should be especially high in patients presenting with other auto-immune conditions.

1.169

EPILEPSY IN DURAL ARTERIOVENOUS FISTULAS (DAVF)

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Rationale: Recent advances of neuroradiology have disclosed more cases of dural arteriovenous fistulas. The abnormal cortical reflux of the lesion is considered to lead to various symptoms including epilepsy. The aim of this study is to clarify the relationship between dAVF and epilepsy.

Methods: We reviewed the cases of dAVF admitted in our institution.

Results: Among 26 cases of dAVF patients admitted in our institution between November 2000 to May 2008, 2 cases were excluded from the study because they were spinal dAVF cases. Age at onset of these 24 cases is 48-76y.o (average 61.9 y.o.). There is one case whose onset of dAVF was epilepsy. In another case, anti epileptic drug (AED) was administered due to unclassified epilepsy 2 years after cerebeller hemorrhage, and dAVF was only diagnosed 2 years after the onset of epilepsy. In 3 other cases, AED was administered in the clinical due course of dAVF.

Conclusions: We have observed that the dAVF can be a cause of localization related epilepsy.

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GENERALIZED-ONSET SEIZURES WITH ALTERNATING LEFT AND RIGHT FOCAL EVOLUTION

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Rationale: Seizure onset determines seizure classification as well as effective therapy. Generalized-onset seizures with focal evolution are uncommon and frequently misdiagnosed as complex partial seizures,

leading to ineffective therapy. We describe generalized absence seizures with alternating focal evolution to either right or left frontal regions in different seizures of the same patient.

Methods: Video-EEG monitoring was used for evaluation of a 12 year old girl with drug-resistant seizures.

Results: Epilepsy started at age 7 years. There was a prior history of febrile seizures at 18 months. Routine EEGs always showed interictal generalized polyspike-and-wave activity and brain MRI was said to be normal. Her seizures at presentation involved staring and eye blinking for 5-10 seconds with daily clusters in the morning. Two years prior to evaluation she developed generalized tonic clonic seizures that started with eye deviation to one side. She was diagnosed with absence and generalized tonic-clonic seizures. However, she failed to respond to multiple anti-epileptic medications including lamotrigine, zonisamide, topiramate and levetiracetam and she was referred for a second opinion. Her neurological exam was normal. Video-EEG monitoring captured frequent episodes of behavioral arrest and eye fluttering in prolonged clusters. On two occasions there was evolution, once with head and eye deviation to the left for 20 seconds then generalized tonic-clonic activity, and once with recurrent head and eye deviation to the right and intermittent right face and right arm twitching for 24 minutes before eventual secondary generalization. The electrographic onset for the first seizure (Figure 1) was 2.5-6 Hz generalized spike-and-wave and polyspike-and-wave activity that evolved to right frontal rhythmic alpha activity, which then became bilateral after 25 seconds. The second seizure electrographic onset was similar to the first (Figure 2), but there was evolution to left hemisphere focal activity that was slower in frequency and wider in field. The prolonged focal activity was repeatedly punctuated by generalized spike-and-wave and polyspike-and-wave bursts. The behavioral arrest and eye fluttering was associated with generalized 2.5-6 Hz spike-and-wave and polyspike-and-wave activity. The interictal discharges was consistently generalized. She was diagnosed with idiopathic generalized epilepsy with generalized absence seizures, and generalized absence seizures with focal evolution and later secondary generalization. She was discharged on levetiracetam 3000 mg per day and valproic acid titration to 2500 mg per day. She was seizure-free at her clinic visit three months following discharge.

Conclusions: Generalized-onset seizures may have focal evolution and be misdiagnosed as partial seizures. Alternating left and right hemisphere evolution of the ictal pattern may occur in idiopathic generalized epilepsy. This phenomenon may be similar to the interictal phenomenon of focal fragments of generalized spike-and-wave discharges, which alternate between the two hemispheres.

IMAGE: images/903375_A.jpg

Figure 1. Generalized spike-and-wave and plyspike-and-wave activity followed by focal left frontal rhythmic alpha activity (underlined in red) in seizure 1. The EEG montage reference is linked ears.

IMAGE: images/903375_B.jpg

Figure 2. Generalized spike-and-wave and polyspike-and-wave activity is followed by left hemisphere rhythmic delta activity in seizure 2. The focal evolution was insidious. The second segment was 4 minutes after the first segment. The EEG montage reference is linked ears.

1.171

EPILEPSY IN ROBERTS SC PHOCOMELIA

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Rationale: Roberts syndrome is a rare autosomal recessive disorder characterized clinically by microcephaly, mental retardation, tetraphocomelia and craniofacial anomalies of varying severity. Karyotype reveals heterochromatic splaying. Roberts SC phocomelia (SC) is a milder phenotype, with milder phocomelia, cloudy corneas and survival to adulthood. Epilepsy has not been previously reported.

Methods: To increased care giver awareness about the epilepsy in SC, records of a patient with 2 different pathogenic point mutations in the sequence of each ESCO2 gene were retrospectively reviewed.

Results: The proband was term, microcephalic, low birth weight and blind with microphthalmia and corneal clouding. Developmental milestones were markedly delayed with poor balance and delayed speech. Partial complex seizures started at age 6 years of age (YO). Seizures have been refractory to all anticonvulsants including divalproex, phenobarbital, pentobarbital, lorazepam, clonazepam, topiramate, oxcarbazepine, phenytoin and zonisamide. The seizures have waxed and waned over the years, becoming secondary generalized after 19 YO. Vagal nerve stimulator was ineffective. Felbatol reduced the seizure frequency to one per month. At 31 YO, brain MRI showed a static diffuse encephalopathy (involving corpus callosum, basal ganglia, brainstem and cerebellum) with numerous small infarct-like lesions in white and gray matter, with relative sparing of the cerebral cortex.

Conclusions: SC is a rare cause of intractable epilepsy. We postulate that the epilepsy is caused by an early onset diffuse encephalopathy due to a segregation defects of chromosomes as seen in primordial dwarfism.

1.172

CALCIFIED CYSTICERCOTIC LESIONS AND MESIAL TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS: PARTNERS IN CRIME

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Rationale: Recent studies have suggested an association between hippocampal sclerosis (HS) and neurocysticercosis (NC). The finding of calcified brain lesions suggestive of inactive cysticercosis in patients with epilepsy and HS may represent an incidental finding. Isolated case reports have shown emergence of HS after resolution of active NC lesions and case series have suggested an increased prevalence of HS in NC. These studies were not controlled for possible confounding factors. We evaluated the association of HS and NC in a case-control study, controlling for possible confounders.

Methods: Patients attending a tertiary referral epilepsy clinic in a large teaching hospital were randomly selected to participate in the study if they presented one of the following types of etiologies: hippocampal sclerosis (HS), focal symptomatic (FS), nonlesional extratemporal focal

epilepsy (NLF) and idiopathic generalized epilepsy (IGE). After collecting clinical, treatment, epidemiological and demographic data, all patients were invited to undergo a head CT. Brain scans were analyzed by a neuroradiologist, blinded to patients' data who noted the presence of calcified lesions suggestive of inactive NC. The frequency of calcified lesions, as well as all other data, was compared between the four groups, by univariate analysis and followed by multivariate analysis.

Results: From 173 patients agreeing to participate the study, 127 were submitted to a head CT. Patients who underwent the head CT were older and had a longer epilepsy duration, in comparison with who did not showed for the head CT, but did not differ with the others parameters, including group. HS group showed a higher prevalence of calcified lesions than the other groups (15/55 or 27.3% X 5/72 or 6.9%; p=0.002). The multivariate analysis revealed that the finding of HS was an independent predictor of the presence of calcified lesions at the head CT (p=0.047, OR=3.2), as well as age>39.5 years (p=0.049; OR=3.4) and previous contact with pigs (p=0.023; OR=4.1). Comparing HS patients with and without NC there was not difference regarding occurrence of an initial precipitating insult (i.e. febrile seizure).

Conclusions: Although it is not possible to establish a cause-effect relationship, we observed an independent relation between hippocampal sclerosis and presence of calcified lesions suggesting inactive NC, controlling for confounders such as socioeconomic status and contact with pigs. The mechanisms involved in this association should be further clarified.

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ASIAN WOMAN PRESENTING WITH NEW ONSET REFRACTORY STATUS EPILEPTICUS : CYCLOPHOSPHAMIDE-RESPONSIVE NMDA RECEPTOR ENCEPHALITIS WITHOUT TUMOR

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Rationale: NMDA receptor auto-antibodies are increasingly recognized as a cause of limbic encephalitis with seizures. Although originally described in association with ovarian teratoma, they are now recognized to occur in association with other neoplasms and even without an identifiable tumor. New Onset Refractory Status Epilepticus (NORSE) is a syndrome first identified in Singapore in which previously healthy young women present in status epilepticus. We describe a young woman presenting with NORSE associated with NMDA receptor autoantibodies but without tumor, who was successfully treated with cyclophosphamide.

Methods: Case report and review of the literature.

Results: A 19 year-old Korean woman presented to the emergency room for a generalized convulsion. The patient had been in excellent health and normal cognitive status until the week previously, then developed emotional lability, echolalia and personality changes over the 3-4 days prior to her first seizure.

She received workup and treatment for presumed meningoencephalitis with LP (WBC 15, otherwise normal), MRI, and 2 courses of acyclovir and empiric antibiotics. CT of Chest/Abdomen/Pelvis with and without contrast was normal. Extensive laboratory workup was negative for meningoencephalitis panel, porphyria, and paraneoplastic panel. She progressively declined in terms of her neurological function, and after 3 weeks was only intermittently verbal, non-ambulatory, unable to take POs, and demonstrated a fluctuating mental status with clinical suggestion of subtle seizures.

Continuous EEG monitoring revealed non-convulsive status epilepticus. The patient was treated with up to 7 anti-epileptics agents and three anesthetic agents (ketamine, propofol and pentobarbital), which initially resulted in burst suppression with generalized periodic epileptiform discharges. Empiric treatment with several courses of IVIG, corticosteroids, and plasmapheresis yielded no improvement. The ketogenic diet was started and a VNS was placed. Nonetheless, she remained in tenuous burst-suppression with occasional breakthrough electrographic seizures for 5 months.

NMDA receptor antibody testing returned as positive. As IVIG, corticosteroids and plasmapheresis yielded no clinical improvement, four pulses of cylcophosphamide were administered. This gradually yielded resolution of epileptiform discharges. The patient improved dramatically over the next month, and is now speaking, eating, ambulating independently with a wheelchair, and participating in rehabilitation after a 9-month acute illness.

Conclusions: In most descriptions of NMDA receptor encephalitis, seizures are responsive to conventional anti-epileptic treatment. In our case, the seizures were extremely refractory to treatment including NMDA antagonist Ketamine, and only resolved when the underlying auto-antibody condition was treated. As such, we propose that some cases previously described as 'NORSE' may in fact be severe, but treatable, cases of NMDA Receptor encephalitis.

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SEIZURES AND QUASI-ICTAL PATTERNS ON DEPTH AND SCALP EEG MONITORING AFTER SUBARACHNOID HEMORRHAGE

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Rationale: Nonconvulsive seizures are frequent after acute brain injury and independently associated with poor outcome. Some seizures on intracranial EEG can not be seen on surface EEG. Quantitative analysis of surface EEG is limited by electrode artifact, which is rare on depth EEG recordings. To report depth and surface EEG findings in poor-grade subarachnoid hemorrhage (SAH) patients.

Methods: Between 6/06 and 4/10, 45 poor grade SAH patients (age 51+/-15 years, 71% women, 80% admission Hunt Hess grade 4-5) underwent multimodality monitoring with microdialysis, brain oxygen tension, cerebral blood flow, and ICP monitoring (duration 6+/- 4 days). Intracortical EEG monitoring with a miniature 8-contact depth electrode (2.5 mm between contact centers) was available in 30 of these patients. Each minute of surface and depth EEG (N=267,683) was categorized separately into non-ictal, on the ictal-interictal continuum including periodic discharges at 2 Hz or faster, or seizures. These categories were assigned based on consensus between two experienced study physicians (JC and LJH).

Results: At any point of the recording surface seizures were seen in 7% of patients (3/45) and ictal-interictal patterns in an additional 16% (N=7). Depth seizures were seen in 37% of patients (11/30) with depth monitoring while an additional 17% of patients (N=5) had ictal-interictal patterns without clear evolution to seizures. Seizures were seen only on the depth in 7,629 minutes from 8 patients (in 85% of these minutes, the surface EEG did not show any ictal patterns, and in

the remainder it was on the ictal interictal continuum). Depth-only ictal-interictal findings were seen in 15 patients, 2 of whom showed ictal-interictal and 3 showed seizures on the scalp at other times during their recording. Surface-only seizures were seen in only one patient (for a total of 47 minutes). However, 93% of this patient's surface seizures (633/678) were detected on the depth electrode and all minutes of surface-only seizures were part of evolving seizure activity that was detected on the depth electrode minutes after being seen on the surface. There was no difference in demographics, admission neurological or CT findings, delayed cerebral ischemia rates, or hospital complications between those with and those without ictal interictal findings or seizures on surface or depth. All 9 patients with depth only ictal-interictal patterns or seizures had poor outcome compared to 3 of 6 patients with ictal interictal or seizure on both depth and surface (OR 4.0; P=0.04). The analysis of multimodality findings is in progress.

Conclusions: Half of patients had seizures or ictal-interictal patterns on intracortical EEG, and the majority of these patterns could not be appreciated on scalp EEG. Ictal patterns isolated to the depth may be associated with poor outcome. Depth EEG monitoring provides high quality, high signal:noise ratio recordings that enables real-time, continuous quantitative EEG monitoring with alarms. Intracortical EEG is a promising component of multimodality monitoring and neurotelemetry in acutely brain injured patients.

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CLINICAL AND GENETIC SPECTRUM OF LAFORA DISEASE IN 104 PATIENTS

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Rationale: Lafora disease is a fatal form of progressive myoclonus epilepsy characterized by the presence of intracellular glycogen-like inclusions. Symptoms start in childhood or adolescence usually with seizures and is followed by rapid and progressive cognitive and motor impairment. Most patients die within a decade of first symptoms. The disease is inherited following an autosomal recessive pattern and in more than 95% of the patients mutations in EPM2A or EPM2B are found.

Methods: We reviewed clinical and genetic information from 104 Lafora disease patients studied in our center between 1996 and 2005, including patients from 26 previously unreported. Genetic analysis was performed by sequencing of the EPM2A and/or EPM2B genes.

Results: One hundred four patients from 82 families were included in the study. Age at onset ranged from 4 to 22 years (mean=12.75±3.5). The most common initial symptom was a generalized tonic-clonic seizure (45%), followed by simple partial occipital seizures (16%), myoclonic seizures (15%) and absences (11%). Photosensitivity was present in 27 out of 36 patients. Cognitive deterioration occurred from 11 to 28 years (15.2±2.47), onset of gait disturbance from 13 to 30 years (16.2±2.8) and inability to walk alone from 13 to 23 years (18.1±2.06). Age at death ranged from 16 to 35 years but 60% of the patients died between 18 and 21 years. Progression of the disease (from first symptom to death) ranged from 4 to 28 years although for 65% of the patients an evolution of 5-9 years was observed. Three patients survived into the fourth decade of life.

Fifty-seven families (70%) had mutations in EPM2A, 23 families (28%) in EPM2B and in 2 families (2.4%) no mutations were found in any of these genes. R241X was the most common mutation in EPM2A and P69A in EPM2B. Skin biopsies did not reveal any abnormalities in three individuals (two with mutations in EPM2A and one with a mutation in EPM2B).

Genotype-phenotype correlations confirmed a milder course of the disease in patients with EPM2B mutations (p=0.034). A significant higher prevalence of simple partial occipital seizures was found in patients with mutations in EPM2A (p=0.021). When patients harboring a homozygous R241X mutation (21 individuals from 15 families) and those with heterozygous R241X mutations (13 individuals from 8 families) were compared, a significant longer progression of the disease (p=0.021) and an older age at which patients died (p=0.014) were found.

Conclusions: The majority of patients with Lafora disease present a fairly homogeneous phenotype although there is wide variability regarding age at onset and patient survival, most patients dying at or before age 21 but with exceptionally high survivals in a few patients. Genetic or environmental factors yet to be discovered may condition a very long progression of the disease. Around 98% of our patients harbor mutations in EPM2A or EPM2B. Patients with EPM2B mutations seem to have a milder course of the disease.

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1.177

LATERALIZING AND LOCALIZING VALUE OF SEIZURE SEMIOLOGY

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Rationale: Seizure semiology is widely accepted as being an important in the presurgical evaluation of patients being considered for resective epilepsy surgery. Whereas individual lateralizing signs (LS) have been previously evaluated for inter-rater reliability and positive predictive value (PPV) they have not been studied in aggregate as patients may exhibit more than one lateralizing sign. Furthermore, the value of semiology to localize the ictal onset zone within a hemisphere has not been measured objectively. Our aim was to objectively study the lateralizing and localizing value of seizure semiology.

Methods: 73 consecutive patients who underwent resective epilepsy surgery between 1999-2007 with Engel class Ia seizure outcome at 1 year were included. Patients who had multilobar resection, hemispherectomy and those younger than 12 years old were excluded. Three observers (PK, AA, DS) were asked to analyze video files blinded to clinical data. They were asked to lateralize seizures based on all available LS including description of auras and neurological deficits. In addition they attempted to localize the seizures to one lobe and within each lobe based on predefined criteria. Agreement of 2 or more observers was required in order to score a particular sign or assign localization. The lateralizing and localizing value of semiology was compared with findings from other presurgical tests (interictal/ictal EEG, MRI, PET).

Results: Table 1 shows the interobserver agreement (Kappa index) and PPV for various lateralizing signs.

19/30 (63%) temporal lobe seizures were correctly lateralized (k=0.64) with correct sublobar localization in 27/30 (90%) patients, k=0.6. Sublobar localization was correct in 12/28 (43%) of patients, k=0.24 (sublobar localization not possible in 2 patients).

20/27 (74%) frontal lobe seizures were correctly lateralized (k=0.55). Lobar localization was correct in 21/27 (78%) patients, k=0.41 and sublobar localization was correct in 5/25(20%) patients, k=0.36 (sublobar classification was not possible in 2 patients).

7/8 (87%) parietal lobe patients were correctly lateralized, k=0.83. Lobar localization was correct in 3/8 (37%) patients, k=0.5.

7/8 (87%) occipital lobe patients were correctly lateralized (k=0.67). Lobar localization was correct in 7/8 (87%) patients, k=0.67.

Figure 1 shows the lateralizing and localizing value of seizure semiology compared with other diagnostic modalities.

Conclusions: Seizure semiology has good lateralizing value particularly in extratemporal epilepsy. Version, focal clonic movements and Figure 4 posturing had high inter-rater agreement and PPV. Localization was highest in temporal and frontal lobe seizures followed by occipital and least for parietal lobe seizures. Semiology appears to have comparable value in terms of lateralization and localization with other diagnostic modalities (MRI, EEG, PET, or SPECT).

LATERALIZING VALUE OF ICTAL SIGNS

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1.178

SPECTROSCOPIC IMAGING OF MTLE AT 7T

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Rationale: The presence of unilateral hippocampal atrophy (HA) in the evaluation of MTLE is often a defining factor that if concordant with the EEG and PET, and is not contraindicated from neuropsychological data, will typically result in candidacy for surgical resection. However, it is possible to have HA without intractable seizures, as seen in familial MTLE (Kobayashi et al 2003). We used ultra-high field MR spectroscopic imaging at 7T to assess MTLE with patients who are all HA positive. We studied n=11 patients who were medically intractable and n=2 patients who were very well controlled (seizure free for >2years on medication).

Methods: Clinical: All patients (n=13) were recruited from the Yale Epilepsy Program. All patients demonstrated hippocampal atrophy on conventional MR imaging (n=9 R HA; n=4 L HA). All except 1 of the 13 patients also had Phase 1 monitoring data that demonstrated clinical and lateralized electrographic changes that were consistent with the side of hippocampal atrophy. One surgical patient who had been seizure free >2 years sought surgical resection for the purposes of medication discontinuation. One non-surgical patient was medically well controlled on monotherapy, and had semiology consistent with medial temporal lobe epilepsy.

Imaging: We used a head only Varian 7T MR system with an 8 element transceiver array for all studies. All acquisitions targeted the medial temporal lobes and were angulated along the planum temporale. A moderate TE40msec spin echo sequence was used to acquire measurements of the singlet resonances including NAA, creatine and choline. This acquisition was used to minimize contributions from overlapping amino acids (glutamate, glutamine). The nominal voxel size is 0.64cc. A single voxel reconstruction technique was used to consistently place the hippocampal spectra in three loci as shown in Fig 1.

Results: Spectral data from a patient are shown in Fig. 1. As a group, the n=11 patients who were medically intractable demonstrated a significantly higher (abnormal) Cr/NAA value in the ipsilateral medial temporal lobe anteriorly in comparison to control (1.06±0.21 patients vs. 0.83±0.04 controls; $p<0.005$, Table). The n=2 patients who were well controlled had values of 0.84 and 0.65, mean 0.74.

Conclusions: Spectroscopic imaging at 7T of medically intractable MTLE is consistent with previous data showing a mean ~28% drop in NAA/Cr in comparison to control. The two patients with MRI documented hippocampal atrophy but who were medically seizure free had NAA/Cr values similar to control. As an evaluation of neuronal mitochondrial function, these data are consistent with the view that NAA/Cr reflects ongoing dysfunction and may be more accurate for an assessment of tissue health than tissue loss directly.

Cr/NAA in intractable MTLE (n=11) vs Control

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$p<0.005$** and $p<0.01$*, significantly different from control

IMAGE: images/906816_A.jpg

Spectroscopic imaging data from a patient with L MTLE. Positions of spectra are circled. The integrated area of NAA is highlighted in spectra 3 and 6.

1.179

LOCALIZATION OF PEDIATRIC SEIZURE SEMIOLOGY: A REVIEW OF 1008 SEIZURES

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Rationale: There is extensive historical and current practical evidence supporting the notion that different seizure semiologies relate to specific anatomical localizations. However, to our knowledge, no systematic analysis of the corresponding electrographic (EEG) data in seizures of different semiology has been reported. The aim of this study was to evaluate the relationship between semiology of seizures in children and adolescenet to the corresponding localization.

Methods: Charts of 225 consecutive pediatric epilepsy patients undergoing Video-EEG monitoring (VEM) over 2 years were reviewed. Seizure semiology recorded during VEM was classified according to ILAE seizure semiology terminology and EEG localization, and analyzed based on onset as defined by the EEG data (generalized, frontal, temporal, parietal, occipital or a combination of different lobes). Statistical analysis (binominal test) was performed using SPSS (version 16.0).

Results: A total of 1008 seizures were analyzed in 225 children, mean age was 8.5 years ± 5.7 (range 0-20), with 50% girls. Auras and seizures with automatisms arose predominantly from the temporal lobes ($p<0.001$). Tonic, clonic and tonic-clonic seizures had most commonly generalized onset ($p<0.001$). Hypomotor seizures were most frequently seen from the frontal lobes ($p<0.001$). Hypermotor seizures had most

commonly multiple lobes or temporal onset ($p<0.001$ and $p<0.05$ respectively). Atonic, myoclonic seizures and spasms had almost exclusively generalized onset ($p<0.001$). Gelastic seizures had only generalized onset ($p<0.001$). Dyscognitive seizures had most commonly generalized or temporal onset ($p<0.001$). Versive seizures had a strong association with multiple lobes being involved at onset ($p<0.001$).

Conclusions: Different seizure semiologies relate to specific brain regions, as identified electrographically. Findings based on EEG provide important information on the seizure epileptogenic zone and seizure propagation, although seizure freedom after resection remains the 'gold standard' for localization. Semiology of seizures can provide important information for epilepsy localization, and should not be overlooked especially in patients undergoing pre-surgical evaluation.

1.180

FOCAL EPILEPSY AND ANTIGAD ANTIBODIES .CLINICAL AND IMMUNOLOGICAL PROFILE

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Rationale: Previous reports have observed an association between focal drug resistant epilepsy and antibodies to glutamic acid decarboxylase (anti-GAD). GAD catalizes the synthesis of gammaaminobutyric acid (GABA) , the mayor inhibitory neurotransmitter in the central nervous system. Anti-GAD are markers for type I diabetes mellitus insulin dependent (DM1) and, in high levels, anti-GAD have been found in several neurological diseases including stiff-person syndrome, cerebelar ataxia, limbic encephalitis, and focal epilepsy.

Purpose: To describe the clinical and immunological profile of a series of patients with temporal lobe epilepsy with anti-GAD

Methods: A basic immunological battery including serum anti-GAD were determined in all patients with cryptogenic temporal lobe epilepsy with age at onset older than 20. Anti-GAD antibodies were analyzed by RIA; values >1UI/ml considered positive. Serum and CSF (when available) of anti-GAD-positive patients were also studied by immunohistochemistry on HEK293 cells transfected with the B1 and B2 subunits of the GABAB receptor (GABABR).

Results: Eight (6 women) of 45 screened patients, were anti-GAD positive (17.7%). Mean age 57 (29-75) years, mean age at epilepsy onset 50 (27-70) years. None reported initial precipitating injury. Brain MRI was pathologic in only 1 patient: right hippocampal hyperintensity on FLAIR sequences. Brain positron emission tomography (PET) with fluodesoxiglucose was done in 2 patients showing unilateral medial temporal hypometabolism. Epilepsy was controlled in 4 patients (<1 seizure/6 month), and considered pharmacoresistant in 4 (50%). Three patients (37.5%) referred important memory impairment since the beginning of the epilepsy and three a mayor depressive episode. Seven patients (87.5%) reported one or more concomitant autoimmune diseases (DM1: 4, hypothyroidism 4, myasthenia 1, rheumatoid arthritis 1, celiac disease 1, lupus 1, polyglandular autoimmune disease 1). One patient with pharmacoresistant epilepsy was treated with corticoids and immunoglobulins with only transient improvement. Anti-GAD levels ranged between 42 and 100.000 UI/ml. CSF, done in 4 patients, did not show positive oligoclonal bands or pleocytosis, The ratio of serum/CSF anti-GAD levels did not support a specific intrathecal synthesis of anti-GAD in any patient. None of the patients had concurrent GABABR antibodies.

Conclusions: Focal epilepsy with antiGAD antibodies is not rare. The epilepsy it is not always pharmacoresistant and is often associated with memory impairment, depression and other autoimmune diseases.

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CHARACTERISTICS OF HIV-INFECTED PATIENTS WITH NEW ONSET SEIZURES

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Rationale: Seizures have been reported to occur at a rate between 3-17% in patients with human immunodeficiency virus (HIV) infection. Such a high percentage, as compared to a normal population, is not surprising. Neurological complications occur in over 50% of patients with acquired immune deficiency syndrome (AIDS). We conducted our research to confirm that the majority of HIV-infected patients with new onset seizures have seizures due to identifiable CNS pathology.

Methods: We retrospectively analyzed The Ohio State University Medical Center (OSUMC) Information Warehouse, an archive of existing medical records and billing data for inpatients and outpatients, over a 3-year period (1/1/2006-12/31/2008). We searched for HIV-infected adults (age greater than 18 years) with new onset seizures using ICD-9 codes for HIV and seizures, epilepsy, or convulsions. We collected demographic information including age at enrollment in the study, gender, the latency between HIV diagnosis and seizure onset, seizure recurrence during the study, presence of HIV antiviral medications at the time of seizure onset, results of investigations for the seizures including electroencephalogram (EEG), neuroimaging, serum laboratories, cerebrospinal fluid (CSF), CD4 cell counts, and HIV RNA viral loads. We divided the study population by etiology of new onset seizure into those related to HIV-related CNS pathology, CNS pathology unrelated to HIV, and other non-CNS etiologies.

Results: Thirty-four HIV-infected adults with new onset seizures were identified. The population included 82% males with a mean age of 41+7.6 years. There was no known etiology for seizure in 14 patients (41.18%). CNS pathology related to HIV was the cause for seizure in 14 patients (41.18%). Seizure due to acute CNS pathology unrelated to HIV was determined in 2 patients (5.88%), and systemic etiology occurred in 4 patients (11.76%). No significant differences between groups were detected regarding CD4 counts and viral loads. The majority of patients had advanced HIV infection with 81.3% with a CD4 count <200 cells/mm^3 preceding seizure and 65.6% with a CD4 count <50 cells/mm^3 preceding seizure. Recurrent seizures occurred in 3 of 30 patients (27.3%) with HIV-related CNS pathology and 13 of 30 patients (68.4%) with other cause for seizure ($p=0.029$). Recurrent seizures occurred in 4 of 30 patients (30.8%) with all CNS pathology versus 12 of 30 patients (70.6%) with other cause for seizure ($p=0.030$).

Conclusions: In the majority of patients, seizure was not related to HIV pathology. A lower percentage of patients with HIV-related CNS pathology had recurrent seizures compared to those with other causes for new onset seizure. This suggests there may be a possible underlying

mechanism of the human immunodeficiency virus itself, rather than CNS pathology, provoking seizures.

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THE ACCURACY OF HYPERVENTILATION AND PARENTAL REPORT IN ASSESSING THE ACTIVITY OF ABSENCE SEIZURES IN CHILDREN

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Rationale: Hyperventilation (HV) is a convenient "bedside" method for eliciting absence seizures (AS) and is often used both to establish a new diagnosis of AS and to monitor the effectiveness of ongoing drug therapy of AS. We set out to measure the sensitivity of HV in two types of "gold standard" groups presumed to have active AS by different criteria: 1) a "high confidence group" of children who manifest spontaneous AS on routine EEG testing (outside of HV) and 2) a "lower confidence group" of children whose AS was judged active by parental report.

Methods: The EEG diagnosis log at Children's Hospital Boston was screened from January 2006 to June 2010 for all patients with 3 Hz generalized spike-wave discharges or absence seizures. The subset of these patients matching ILAE criteria for childhood or juvenile absence epilepsy formed the study group (n=68). Two comparative "gold standard" groups of EEGs (all with adequate HV) in children with presumed active AS were formed: 1) those EEGs which showed spontaneous AS (outside of HV) and 2) those EEGs done at a time that the child's parents reported active AS in their child. Hyperventilation was carried out for a minimum of 3 minutes. An AS was defined as an episode of generalized spike-wave discharges associated with clinical change or unresponsiveness.

Results: 53 EEGs that captured spontaneous AS were found in which HV was also done (in 44 unique patients). In 41 (77%) of these EEGs HV also elicited an episode of AS (71% of those untreated [n=28] and 84% of those treated [n=25] at the time of the EEG). 95 EEGs were identified (in 55 unique patients) whose parents reported active AS at the time of the EEG. Of these, HV elicited AS in 59 (62%) EEGs (71% of those untreated [n=41] and 56% of those treated [n=54]). Of the 84 EEGs done at a time that parents reported no active AS, AS was seen spontaneously or during HV in 30 (36%) tracings.

Conclusions: Even in children with active AS by the strict criterion of the occurrence of spontaneous AS in the EEG, only 77% had an AS during HV, implying that this technique will miss approximately one quarter of children with active AS. When positive parental report was used as the "gold standard" for presumed active AS, only 62% of children manifested AS during HV; the different rates imply that parents may overestimate the activity of AS approximately one quarter of the time in children who are effectively treated. Conversely, in patients in whom AS was definitely still active by EEG criteria, parents underreported AS activity 36% of the time. This percentage represents a minimum estimate since some children with active AS may not have exhibited their seizures during the period of the EEG recording. These findings imply that parental report has an approximate false-positive rate of one quarter and an approximate false-negative rate of more than one third.

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ICTAL LIP-SMACKING IN TEMPORAL LOBE EPILEPSY HAS A STEREOTYPED ELECTROGRAPHIC SIGNATURE

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Rationale: There is evidence that seizures do not propagate diffusely or randomly, but rather, in a preferred order to involve a specific set of brain regions. Also, patients with focal seizures tend to exhibit stereotyped behaviors. However, the relationship between the neuroanatomy of seizure propagation and stereotypy of ictal behaviors remains poorly understood. The current study was designed to study the stereotypy of ictal behavior in a group of patients with focal medial temporal lobe epilepsy (MTLE), and to determine if there is a specific electrographic correlate to the onset of any ictal behavior.

Methods: In 55 seizures recorded with scalp or intracranial electrodes in 10 patients with verified MTLE, the type, duration, and order of exhibited behaviors were documented. Using T-test, ANOVA, frequency-cluster-matrix analysis, and rule-mining-test we measured the commonality and directionality of ictal behaviors. For electrophysiological analysis, we used Hilbert-transform, phase locking-value, modulation-index, coherence, and synchronization-likelihood.

Results: 1) a specific somatotopical subset of behaviors occurs in MTLE; 2) ictal behaviors are related to each other in time; lip-smacking always precedes arm/hand movement or vocalization; 3) lip-smacking starts 59±10secs after the initial seizure onset in the MTL; and 4) the onset of lip-smacking is always associated with a strong synchrony between ipsilateral hippocampal and inferior-lateral temporal lobe (ILTL) activity in the theta band frequency domain.

Conclusions: Our findings support the notion of behavioral and electrophysiological stereotypy across a population of patients with focal epilepsy, and suggest that MTL activity is insufficient to generate the ictal behavior of lipsmacking. Recruitment of the ILTL in the theta band frequency domain seems to correlate in time with the onset of lipsmacking.

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PARIETAL LOBE EPILEPSY: GREAT IMITATOR AMONG FOCAL EPILEPSIES

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Rationale: Parietal lobe comprises large areas of association cortex extensively connected to other lobes. We hypothesize such widespread network projections can produce erroneous localization and misinterpretation of scalp EEG and clinical semiology in parietal lobe epilepsies (PLE). We investigated the reliability of electroclinical features in PLE as compared to frontal (FLE) and temporal lobe epilepsy (TLE).

Methods: Fifty consecutive pharmacoresistant focal epilepsy patients seizure free for e" 12 months (median 23 months; IQR 14.75-35.75) following resections limited to frontal, temporal or parietal lobe were identified. Interictal EEG discharges (iiEEG), single representative ictal EEG (iEEG) and seizure video were extracted from archived files of

scalp video EEG monitoring (median 5 days; IQR 4-6). Two raters (R1 R2) blinded to other clinical data independently reviewed the EEG. Seizure videos were then presented and raters formulated their clinical impression (CI) based on all findings to either PLE/TLE/FLE/non-specified. Patients with more than one iEEG and previous neurosurgery were excluded.

Results: 16 PLE, 17 FLE and 17 TLE patients were studied. Groups did not differ significantly in demographics, absence of iiEEG (5 FLE, 2 TLE, and 3 PLE), epilepsy onset or presence of normal MRI (4 FLE, 1 PLE). Interobserver agreement was substantial across different aspects of the iiEEG (ê .79-.96). PLE iiEEG showed greatest scatter outside the lobe of origin: unilateral iiEEG in anterotemporal region (electrodes (ele) Sp/FT, n=7); unilateral iiEEG in parietal region (P ele, n=6); unilateral frontopolar or bilateral frontal iiEEG (Fp ele, n=3); iiEEG central region (Cz ele, n=2) in 2; and contralateral iiEEG in anterotemporal region (n=5). FLE group did not show contralateral iiEEG and were generalized (bifrontal maximal, n=5), frontopolar (n=3), parasagittal frontal (n=2) and central (n=3). TLE iiEEG showed most consistent lobar localization: ipsilateral anterotemporal (n=10), ipsilateral temporal (T7/8 ele, n=6), ipsilateral frontopolar (n=4) and contralateral anterotemporal (n=3). There was a significant difference in number of iiEEG populations between PLE (median 2; IQR 1-2.75) and FLE (median 1; IQR 0-1) (p=.032). Interobserver agreement of iEEG was substantial (ê .61; p<0.005). Raters were able to localize and lateralize iEEG to the epileptogenic region in all TLE (R1,R2), (R1-11/17; R2-15/17) FLE and (R1-7/16; R2-10/16) PLE patients (p=.002; p=.011). CI agreement for all epilepsy types was moderate (ê .58; p<.005). In patients whereby raters confidently categorized their CI to one epilepsy type, PLE was often misidentified (ê .52; p=.002): R1 correct/specified FLE 8/8, TLE 12/14, PLE 4/8; p=.034); R2 (FLE 14/14, TLE 13/13, PLE 6/10; p=.002). TLE (R1 correctly identified/rest 14/17; R2 13/17) are more often accurately localized compared with PLE (R1 4/16; R2 6/16) (p=.032; p=.013).

Conclusions: Interictal and ictal recordings are likely to be more falsely localizing and/or mislateralizing in patients with PLE as compared to patients with FLE and TLE.

1.185

HOW HELPFUL ARE REPEAT EPILEPSY MONITORING UNIT ADMISSIONS AFTER AN INITIAL NONDIAGNOSTIC EVALUATION?

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Rationale: Video EEG (VEEG) monitoring is expensive and sometimes a typical event is not recorded so a definitive diagnosis is not made after one prolonged admission. The primary purpose of this study is to determine the utility of repeat epilepsy monitoring unit (EMU) admissions for spell characterization after an initial e" 5 day nondiagnostic evaluation. Previous studies found that 48-72 hours of monitoring was usually sufficient for diagnosis in most patients with only a minority of cases requiring more than one week for establishing a diagnosis.

Methods: On retrospective review of 4663 admissions between1998-2010, we identified 43 patients who were readmitted for characterization of their spells after an initial nondiagnostic e" 5 day evaluation. A patient's evaluation was considered nondiagnostic when a typical spell was not captured and there was no objective evidence of epilepsy based on video EEG monitoring and the clinical history. Patients with interictal spikes were included if these cases were still considered nondiagnostic when the history and interictal EEG did not correlate.

Results: Of 43 patients included in this study, 18 (41%) had diagnostic repeat evaluations. Interictal spikes occurred in 6 of 43 during the initial evaluation. On repeat 2-8 day evaluations of these patients, 3(50%) were diagnosed with epilepsy and 3(50%) remained nondiagnostic.

Out of 37 with no interictal discharges during the initial admission, 15(40.5%) had a diagnostic repeat evaluation. Of these, 9 were diagnosed with psychogenic nonepileptic seizures (PNES), 4 with epileptic seizures and 2 had interictal spikes and only PNES. In these 37 cases, mean length of monitoring for initial evaluation was 8.2 days (range 5-16), and for second evaluation it was 6 days (range 2-15). Three admissions were performed in 9 patients with length of monitoring ranging form 2-20 days.

We found that 32/43 (74%) of the study cases included were female. Compared to the entire database population at our center, 640/902 (71%) of patients with nonepileptic seizures were female and in the patients with proven epilepsy 880/1615 (54%) were female.

Conclusions: These data justify a repeat, and sometimes prolonged, VEEG evaluation in patients with an initial nondiagnostic EMU evaluation for 5 or more days. Repeat admissions allowed 41% of cases to have diagnostic findings to characterize seizures or spells. A high proportion of patients with an initial e" 5 day EMU evaluation are female. When a diagnosis is made on subsequent admissions in patients without spikes in the first admission, most have PNES.

1.186

MEASUREMENT OF QT INTERVALS DURING ELECTROENCEPHALOGRAM (EEG) TESTING: ARE THEY RELIABLE?

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Rationale: To compare the accuracy of EEG -QT measurements with simultaneous 12 lead EKG-QT in pediatric patients as a quality improvement initiative.

Methods: Prospective QT measurements from simultaneous 12 lead EKGs were compared with EEG QT (n=22). Indications for EEGs included paroxysmal spells (n=9), primary seizure disorder (n=11) or syncope(n=2). EEGs were recorded digitally at the standard paper speed of 30 mm/ sec at a gain of 7 mm/µv. The QT interval from 10 second print out of a single lead EKG (Lead I) was measured manually. Measurements were made by two different technicians and a neurologist for inter-observer variability and averaged. A standard 12 lead EKG was recorded at a paper speed of 25 mm/sec and a gain of 10mm/µv. Average of 3 measurements of the QT interval from leads I, II and V5 were calculated by a cardiac electrophysiologist.

Statistics: Paired t-test was performed to compare the difference between individual and average EEG-QT and EKG-QT intervals. A p-value of <0.05 was considered to be statistically significant.

Results: Mean age of subjects was 8.1 years (range 5m-15years). There were 14 males (64%). Inter observer variability in EEG-QT measurements was present between the 2 technician readings in 19/22 patients (86%)(mean difference 20 ms; range 10-50 ms) but not between one of the technicians and the physician. The average of 2 measurements of EEG-QT intervals (276±30ms) was significantly shorter in comparison to EKG-QT (310±30ms) ($p<0.0001$). Due to the presence of significant inter-observer variability, EEG-QT obtained by individual EEG technicians were also compared with EKG-QT. These were also significantly shorter. (Tech 1: 280±40 ms; Tech 2 and neurologist: 272±30ms) ($p<0.0001$).

Conclusions: There is high inter-observer variability and a shorter QT interval with under estimation of up to 55 ms in the EEG- QT compared to EKG -QT, making such measurements unreliable. Different paper speeds, signal gain and difficulties in identifying the termination of T wave could be potential factors causing these differences. We therefore recommend that EKG during routine EEG recordings be used to detect artifacts and not for determination of QT intervals.

1.187

CLINICAL FEATURES OF STATUS EPILEPTICUS IN CHILDREN

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Rationale: Status Epilepticus is a life-threatening medical emergency which requires early recognition and aggressive treatment. In this study, we examined the clinical features of children presenting with Status Epilepticus (SE) in a single tertiary care center.

Methods: Retrospective chart review was performed for all children (age: 0-18 years) diagnosed with SE at Texas Children's Hospital (2002-2010) that were included in the neurology database. The clinical and demographic features, diagnostic tests utilized, and treatment responses were analyzed.

Results: A total of 313 children were identified; 34 charts were unavailable for review. In the remaining 279 children [M/F: 162 (58%)/ 117 (42%)], mean age was 3.9+/-4.0 (range: 0-17 years). Febrile SE (FSE) occurred in 106 (38%); acute symptomatic etiology occurred in 71 (25%), and remote symptomatic in 102 (37%). Acute symptomatic etiology included CNS infection in 7%, trauma in 3%, metabolic (3%), genetic-inborn errors (9%), and hypoxia/ischemia in 16%. Non-convulsive SE (NCSE) occurred in 12 (4.3%) and newborn SE in 6 (2.2%).

Duration of prolonged seizures ranged between 8 to 180 minutes (mean: 38.1-31.7). SE was longer than 60 minutes [refractory SE (RSE)] in 21 (7.5%) despite the administration of more than 2 conventional (first-line) antiepileptic drugs (AEDs). Repetitive seizures without a return to baseline mental status occurred in 91 (32.6%). Focal clinical features were reported by care givers or health professionals in 51 (18.3%). Fever was present at the time or within 24 hours prior to presentation in 133 (47.7%). A prior history of a febrile seizure occurred in 43 (15.4%), epilepsy in 78 (27.9%) and pre-existing neurological problems in 102 (35%). Recurrent SE developed in 46 (16.5%).

EEG was obtained in 187 (67%); of these, continuous EEG-video (CEEG) monitoring was performed in 36 (12.9%).

For first line AEDs, diazepam was administered in 49 (17.6%), lorazepam in 156 (55.9%), fosphenytoin in 147 (52.7%) and phenobarbital in 74 (26.5%). For fourth line AEDs, a single or continuous midazolam dose was required in 27 (9.7%) and pentobarbital in 13 (4.7%). Fourth-line AEDs were therefore needed in 40 (14.3%). The mortality rate was 3.5% (10/279) overall and 23% in RSE (5/21).

Conclusions: Our clinical experience with status epilepticus from a single tertiary care center is consistent with previous studies of SE in children. We found that 1/3 of the children with SE had repetitive brief seizures and fourth-line AEDs were needed in 14.3% of children treated for SE.

1.188

SOCIOECONOMIC STATUS AND SELF-MANAGEMENT IN EPILEPSY: COMPARISON OF DIVERSE CLINICAL POPULATIONS IN HOUSTON, TEXAS

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Rationale: A number of studies provide evidence that minorities and low-income people with epilepsy receive different amounts and types of healthcare compared to non-minority, upper-income populations. The need to understand the reasons for disparities is important to advocates and policy makers seeking to eliminate inequalities in epilepsy care. The focus of the project is on two questions. 1) Are there disparities in self-management behavior and associated psycho-social factors between patient populations of different socio-economic status (SES)? 2) Does the relationship between psychosocial factors and self-management vary by SES? Answers to such questions are needed to help inform program administrators, clinicians, and policy makers of the nature of disparities that exist among people living with epilepsy and the potential impact of strategies to reduce or eliminate them.

Methods: We systematically recruited patients from a public hospital clinic in Houston, Texas that serves a predominantly low-income, minority, uninsured population, and a private free-standing clinic that serves a more balanced racial/ethnic and higher socioeconomic status population that is mostly insured. The patients at each site completed a questionnaire on self-management behavior and a number of related psycho-social factors including self-efficacy, knowledge, depression, social support, satisfaction, stigma, desire for control, and outcome expectations. Bivariate statistics were derived comparing differences by site in self-management and psycho-social characteristics of patients. Multivariate models were estimated to examine the relative importance of SES in the relationship between self-management and the psycho-social factors adjusted for demographic and clinical characteristics.

Results: The average scores on overall self-management and the self-management sub-scales of information management and safety management were higher for the low-SES group compared to the high-SES group (per item average on a 5-point scale, 3.75 vs 3.63, $p<.03$). There was no difference found for medication management, seizure management, and lifestyle management. The scale scores for the various psycho-social factors were all significantly different between the groups ($p<.01$). However, two of the factors, self-efficacy and social support, were strongly associated with self-management in both patient groups (Pearson coefficients .43 and .31 for self-efficacy, and .30 and .20 for social support). In a multivariate model, we found that these

two factors remained strongly associated with self-management ($p<.05$) after controlling for demographic and seizure frequency characteristics of the patients.

Conclusions: The self-management behavior of low-SES patients is equal to or greater than that of low-SES patients. There is a strong association between self-efficacy, social support, and self-management. The relationship was not significantly affected by SES differences between the groups suggesting that similar strategies to improve self-management may be applicable across diverse populations.

1.189

EFFICACY AND SAFETY OF RAPID MEDICATION REDUCTION IN THE EPILEPSY MONITORING UNIT

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Rationale: Inpatient video EEG monitoring is a critical tool for characterizing paroxysmal events as epileptic or non-epileptic and for localizing seizures in order to guide therapeutic decisions. It is often necessary to capture events through discontinuation or reduction of antiepileptic drugs (AEDs), but there are no guidelines as to how quickly or to what degree they can be reduced to limit length of stay without challenging patient safety. This study describes our experience tapering AEDs beginning with the morning dose prior to admission to the epilepsy monitoring unit (EMU).

Methods: We conducted a retrospective chart review of patients admitted to our EMU during 2009. Background information collected included age, sex, and history of status epilepticus or convulsion. According to our standard practice, patients were contacted by phone the week prior to admission to update seizure history. Patients who were without daily seizures, who had no history of status epilepticus, and for whom admission prior to 2pm was feasible were instructed to hold their morning dose the day of admission and given a reduced AED dosage once in the EMU. We determined length of stay, amount of AED reduction, and time from admission to dose nadir and first typical event. Complications were noted and included seizure prior to admission or to EEG hook-up and status epilepticus. Yield of seizure recording was also determined.

Results: There were 125 admissions to our EMU in 2009. Among them, 115 were for recording of clinical events. Eighty-two of the 115 were women (71%). Mean age was 40 years (range 17-76). In 39 patients (34%), AEDs were stopped with the 8am dose and, in 40 patients (35%), the AED dose was reduced with the 8am dose. Twenty patients (17%) were not taking an AED. In 8 patients, AEDs were tapered after admission. The remaining 8 had no dose reduction.

Eighty-five patients (74%) had a typical event recorded. The mean length of stay was 74.3 hours (range 25.4 to 525.8). The mean time from admission to dose nadir was 9.1 hours (range 0 to 102.5). The mean time from admission to first typical event was 15.9 hours (range 0.6 to 68). Fifty patients (43%) were discharged with a diagnosis of epilepsy and 38 (33%) of non-epileptic events. Four patients with epilepsy were found to also have non-epileptic events. In 27 patients (24%), a definitive diagnosis could not be made.

One patient with a history of daily seizures had a non-convulsive seizure in the hours prior to admission. Another had a non-convulsive seizure between admission and EEG hook-up which was only captured on video. None of the patients were found to be in status epilepticus upon or during the admission.

Conclusions: In an EMU with scheduled admissions before 2PM and updated information regarding seizure type and frequency, AEDs can safely be held or reduced the morning of admission. In our practice, this has led to a mean length of stay of 3.1 days (74.3 hours) with a 74% efficiency of recording typical events.

1.190

THE UTILITY OF PRESURGICAL EVALUATION WITH FORAMEN OVALE ELECTRODES

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Rationale: Recent data suggests that scalp EEG monitoring may be sufficient for presurgical ictal localization in patients with intractable epilepsy and with mesial temporal sclerosis (MTS) on MRI. However the MTS region may not be the sole epileptogenic region. EEG evaluation with foramen ovale electrodes (FOEs) provides a minimally invasive and more sensitive way to record ictal discharges from mesial temporal structures. FOE monitoring can also eliminate the need for more invasive forms of intracranial EEG recording. In this study, we reviewed consecutive cases of presurgical video EEG patients undergoing FOE monitoring and compared the conclusions after phase 1 (scalp) and phase II (scalp and FOE) video EEG.

Methods: Fifty patients that underwent evaluation with FOEs were retrospectively reviewed. The cases were subdivided into three groups: Group A - MTS established by MRI (n=25), Group B - potentially epileptogenic brain lesions other than MTS (n=13), and Group C - no MRI lesions (n= 12). We quantified the number of cases where discordant findings were discovered by FOE monitoring . Discordance was defined as seizure onset from regions other than the area of structural brain lesion. In non lesional patients, discordance was defined as FOE seizure onset differing from seizure onset suggested by clinical and electrographic features during scalp EEG monitoring. Surgical outcome was categorized using Engel's Classification of Postoperative Outcome with Class1a and 1b considered a good surgical outcome.

Results: Six of the 25 patients with MTS (Group A) showed seizure onset localization on FOE monitoring that were discordant with MRI findings. The group included cases with bitemporal, extratemporal, and multifocal ictal onsets. All 13 of the 19 concordant MTS patients had tailored temporal lobectomies with good surgical outcomes. Five of the 13 patients with other brain lesions (Group B) had findings on FOE monitoring that were discordant with expected ictal localization. Of the 8 concordant patients, 6 went to surgery and 4 had good surgical outcomes. Finally, 1 of the 12 patients with nonlesional epilepsy (Group C) had discordant findings consisting of bitemporal seizure onsets.

Conclusions: EEG monitoring with FOEs provides a minimally invasive method of recording ictal discharges from mesial temporal structures. These data suggest that up to 24% of patients with MTS can have seizure onsets from areas other than the region of MRI abnormality and that these onsets can be detected by FOEs. 19 of the total 21 patients receiving FOE monitoring and epilepsy surgery had good surgical outcomes in this series. Nonlesional patients in this group were not always good surgical candidates for other reasons. FOE monitoring can also be useful in patients with seizure semiology suggestive of mesial temporal onset but with other potentially epileptogenic brain lesions. It may demonstrate mesial temporal onset and rule out the need for more invasive EEG monitoring. FOE monitoring is a helpful, minimally invasive tool in the surgical evaluation of patients with and without MTS on brain MRI.

1.191

PROBABILITY OF DEVELOPING EPILEPSY IN PEDIATRIC ARTERIAL ISCHEMIC STROKE

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Rationale: Previous studies have reported variable rates of epilepsy in both childhood and neonatal arterial ischemic stroke (AIS). We sought to evaluate the probability of developing epilepsy in perinatal and childhood stroke in a combined prospective/retrospective cohort of the children from The Children's Hospital, Denver.

Methods: From August 2006 through January 2010, we collected data on clinical presentation, seizure onset, seizure recurrence, and development of refractory epilepsy in 104 consecutively enrolled children with AIS. Patients were classified as childhood AIS (age 29 days - 18 years inclusive), perinatal AIS (PAS- defined as symptomatic AIS presenting at birth - 28 days), or presumed perinatal stroke (PPAIS- defined as chronic presentation of a focal deficit corresponding to a chronic/remote infarct on neuroimaging). Early seizure after stroke was defined as within one week after stroke diagnosis. Epilepsy was defined as two or more seizures separated by 24 hours occurring greater than one week after stroke diagnosis. Kaplan-Meier survival analysis was performed to compare time to onset of epilepsy in those with AIS versus PAS/PPAIS.

Results: Of the 104 patients with AIS, 52 met criteria for childhood AIS (50%) and 52 for PAS/PPAIS. Median follow-up time was 16.7 months (IQR: 6.9 mo - 41.6 mo) in childhood AIS and 28.5 months (IQR: 10.0 mo - 52.2 mo) months in PAS/PPAIS. A total of 55 patients (53% of the cohort) had seizures (20 childhood AIS, 35 PAS/PPAIS) and only 18.3% of the entire cohort developed epilepsy (11 childhood AIS and 8 PAS/PPAIS). Two childhood AIS patients had recurrent AIS. Of note, one of these patients had epilepsy, and was only counted once. Two patients (1.9%) became refractory. One was in the childhood AIS category and the other in the PAS/PPAIS group.

Survival analysis revealed that the probability of epilepsy-free survival at 12 months did not differ between childhood AIS and PPAIS cases; 84% versus 82%, respectively; log rank P=0.79. Very few patients developed new-onset epilepsy beyond 12 months (1 in the AIS groups at 24 months, and 2 in the PAS/PPAIS group at 21 and 30 months).

Conclusions: Risk of epilepsy is high following pediatric stroke, at approximately 20%, and does not appreciably differ between childhood AIS and PAS/PPAIS. However, seizures at diagnosis are more common in PAS/PPAIS. Larger prospective studies are needed to confirm these results and inform seizure management recommendations in perinatal AIS.

To our knowledge, this is the first report of the probability of developing epilepsy in a combined perinatal and childhood AIS using survival analysis.

IMAGE: images/907927_A.jpg

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USE OF EEG SPECTRAL ANALYSIS IN PREDICTING DEVELOPMENT DELAY IN INFANTS

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Rationale: There is increasing evidence that there is a strong relationship between brain oscillation dysfunction and cognitive impairment. The goal of this study was to determine if frequency and power of EEG background activity are independent predictors of developmental impairment in infants.

Methods: We examined the EEGs of 200 consecutive infants between 6-24 months who were referred for an outpatient EEG because of epilepsy or suspected seizures. An electroencephalographer blinded to developmental assessment evaluated two 5 second epochs of EEG free of artifacts during the awake and sleep states. Because of normal age-related changes in frequency and power of oscillations, the infants were stratified into three age groups: 6-12 months (n=86), 12-18 months (n=65) and 18-24 months(n=49). Based on review of the medical records by an author blinded to EEG data, developmental assessments were classified as normal, moderate and severe.

Results: Significant differences between groups were found in the awake recordings: i) In the 6-12 month old group with moderate or severe developmental delay a lower mean frequency, greater delta and less theta power was seen than in the normal group; ii) In the 13-18 month old group, theta power was significantly lower in the moderate and severe developmental delay groups compared to the normal group,; iii) In the 18-24 month old group, alpha power was significantly lower in the moderate and severe developmental delay group than the controls. During sleep no significant difference in mean, peak or median frequency or power of alpha, delta, theta and beta were seen in any of the three age groups between the children with normal development and those with severe or moderate delays.

Conclusions: This study demonstrates that frequency and power of brain oscillations during wakefulness in infants is a powerful predictor of neurological development. The findings support the notion that normal oscillatory activity is critical for normal cognitive function during development.

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CLASSIFICATION OF GENERALIZED TONIC-CLONIC SEIZURES ONLY: FOCAL OR GENERALIZED?

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Rationale: New-onset generalized tonic-clonic seizures (GTCS) only without focal features in teenagers and young adult are considered to be primarily generalized unless proven otherwise. It is not certain whether the seizure is truly of generalized or focal origin in patients with GTCS only. We attempted to establish the epilepsy classification, based on EEG and MRI findings in patients with GTCS only without focal features. We retrospectively analyzed clinical characteristics of patients with GTCS only.

Methods: We included patients with at least two attacks of GTCS only who underwent scalp EEG and MRI evaluation from Yonsei Epilepsy Registry database which had been documented by a physician between

1999 and 2009. We excluded patients with 1) significant etiological factors except for febrile seizures and family history of epilepsy 2) mental retardation or focal neurological deficits, 3) focal ictal features, such as aura, loss of responsiveness without convulsive movements, conscious head version, and conscious or unconscious focal convulsive movements involving unilateral face or extremities, 4) GTCS only during sleep, and 5) occurrence of focal features on ictal semiology or EEG during the follow-up.

Results: A total of 60 patients were selected. Mean number of EEG evaluations was 2 (1 to 5) per patient. Focal or generalized epileptiform discharges on EEG were found in 28% of patients (17/60). Focal structural abnormalities on brain MRI were demonstrated in 13% of patients (8/60). The patients were divided into three groups according to EEG and MRI findings. Group A with generalized epileptiform discharges and normal MRI (strict criteria of generalized epilepsy) consisted of seven patients (11.7%), and their mean age of onset was 18.7±5.7 years (range 12 to 30). Group B with normal EEG and MRI was 37 patients (61.7%), and their mean age of onset was 24.8±13.0 (range 1 to 55). Group C with focal epileptiform discharges or abnormal MRI was 16 patients (26.7%), and their mean age of onset was 34.3±19.0 (range 14 to 69). All patients of group A were under age of 30 years of onset. The onset age of group A was significantly earlier than group C (p=0.038). There was no difference in age of onset between group A and B, and between group B and C. In group C, 56% of patients (9/16) showed focal epileptiform discharges or structural abnormalities in the frontal region.

Conclusions: Despite of small sample size, this study suggests that patients with semiologically primarily GTCS had either focal or generalized origin, as expected. The age of onset in addition to EEG and MRI findings may be helpful in differential diagnosis between focal and generalized origin. However, if strict criteria of generalized epilepsy are considered, epilepsy classification may not be possible in the majority of patients with GTCS only.

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A PROSPECTIVE LOOK AT POST TRAUMATIC SEIZURES IN A PEDIATRIC TRAUMATIC BRAIN INJURY POPULATION

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Rationale: Traumatic brain injury (TBI) in the pediatric population is a significant cause of morbidity and mortality. One form of morbidity is posttraumatic seizures that can be seen early (<7 days) or late (>7 days) after an injury. While subclinical seizures have been reported in patients after TBI, the incidence, risk factors and subsequent effects are unknown in children. Our primary goal is to determine the frequency of subclinical and clinical early post-traumatic seizures (EPTS) in children with moderate-severe TBI, using continuous video EEG monitoring. Secondary goals are to evaluate the risk factors for EPTS and to measure the global functional outcomes of those children with EPTS.

Methods: In January 2009 we began to prospectively track all consecutive pediatric patients admitted to UCLA for TBI. Continuous video EEG monitoring was initiated at the time of admission for 24 hours and extended if seizures were captured. In addition we collected comprehensive data including demographics, hourly physiological data, CT scan results and performed global outcome. We are continuing to follow these patients after discharge.

Results: To date, 40 patients have been consented (13 females and 27 males), 3 mild, 31 moderate and 6 severe TBI, ages 0.2-17.2 years. Fall was the most common mechanism followed by motor vehicle accident and inflicted TBI. Early PTS was documented in 12 (30%) patients. No relationships were found between injury severity, EPTS, age at injury and intraaxial blood. Subclinical seizures were seen in 3 (7.5%) patients, all less than 0.6 years old. All had moderate severity, fracture on CT scan and intraaxial blood. All seizures were focal and two of the patients had interictal findings in similar locations. All 3 patients had multiple seizures during the first 24 hours of the study, and one was in subclinical status epilepticus with seizures lasting up to 90 minutes.

Conclusions: Seizures, both clinical and subclinical are seen in a significant proportion of pediatric patients after TBI. In our cohort, of which the majority was moderate in severity, 30% had EPTS and 7.5% had subclinical EPTS. The 3 patients with subclinical seizures did not have clinical seizures, and without video EEG monitoring these would have gone undiagnosed. In our study, subclinical seizures were only seen in infants. The absence of statistically significant additional risk factors may be related to the small population as well as the large number of moderate injuries to the general exclusion of other severities, an unexpected finding. Future investigations of this cohort will seek to identify risk factors for EPTS and LPTS, the relationship between early physiological disturbances and EPTS and the effect of PTS on long term outcomes. Seizures, both clinical and subclinical, are seen in a significant proportion of pediatric patients after TBI. Continuous video EEG monitoring may be required to properly diagnose all of these patients.

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INVESTIGATIONS ORDERED IN ADULTS WITH EPILEPSY IN TERTIARY CARE

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Rationale: To understand patterns of epilepsy care at the primary and tertiary level one must assess investigations and management at each level, and variables that determine clinician behavior. We analyzed prior and new investigations after a 1st visit at our epilepsy centre, and variables associated with these decisions.

Methods: The Calgary Division of Neurology is the main tertiary referral centre for adults with epilepsy, serving 1.3 million people. We prospectively captured data on consecutive adults with the diagnosis of epilepsy at the 1st encounter in our outpatient epilepsy program, using a validated data capture and verification system, excluding patients with single seizures and children. We captured type and number of investigations done prior to referral and new investigations triggered by the 1st encounter in the epilepsy program and analyzed factors associated with these decisions.

Results: In 687 consecutive patients (52% women) the mean age and duration of epilepsy was 40 and 12 years respectively, 64.1% had focal epilepsy, 23% had idiopathic generalized epilepsy, and 21% were seizure free in the past year. At the time of the 1st visit, 83% and 61% already had an EEG and MRI, respectively. Video-EEG and neuropsychological tests had been done each in 7%. Patients with focal seizures, as compared to other seizures, were 20% more likely to have had an MRI (p0.005), but just as likely to have had a CT head (60%), and routine (80%) and sleep deprived (20%) EEG. New investigations

were ordered in 70% of patients as follows: Scalp EEG (52%), MRI (38 %), video-EEG (7%), CT head (2%). The probability of new tests did not vary by type of seizure or epilepsy syndrome (60%-70%), but in pair-wise comparisons new tests were ordered in fewer patients with localization related epilepsy (RR=0.85, p=0.009), and in more patients with GTC seizures (CT, MRI, routine EEG) (RR=1.13, p=0.04). The most frequently repeated investigations were routine EEG (49%), MRI (27%) and video-EEG (26%). In contras CT was ordered in 2%. Seizure freedom in the past year did not influence the decision to order new tests. But previous findings strongly influenced the probability of repeating a test. A repeat MRI was ordered only in 23% of patients with a previously abnormal MRI, but in 53% with previously normal MRIs ($p<0.001$). Repeat EEG and MRI were more likely in patients with focal epilepsy and unknown seizure focus (64% for EEG, 45% for MRI).

Conclusions: Up to 17% of patients have no EEG and 39% have no MRI prior to referral to tertiary care, and investigations are ordered in 70% after assessment. Patients with any GTCs get more outpatient investigations after the 1st visit than those with focal seizures. The causes remain to be determined. The most important predictor of new investigations is not lack of seizure control, but uncertainty of localization of seizure focus and previous findings on EEG and MRI. CT is used broadly by referring clinicians, but rarely by epilepsy specialists. There is a need for systematic studies assessing investigations for epilepsy and their yield in primary and in tertiary care settings.

1.196

ARE CHILDREN WITH TEMPORAL LOBE EPILEPSY AT INCREASED RISK FOR OBESITY?

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Rationale: Obesity is a significant public health problem. Children with epilepsy may be at increased risk for overweight and obesity due to antiepileptic medications, physical inactivity and neuroendocrine factors. We studied the rate of obesity in children with temporal lobe epilepsy and analysed weight changes after epilepsy surgery.

Methods: We identified 108 children aged 2 years to 18 years with temporal lobe epilepsy, who underwent temporal lobe resection between 1998 to 2009. A retrospective data analyses included weight, height and BMI index prior and 2 years post surgery, age of seizure onset, age at surgery, seizure frequencies, mesial or lateral temporal pathology.

Results: Mean patient age at temporal lobectomy was 12.1 years (range 2 to 18 years), 85% had mesial temporal limbic structures removed. Pathology included hippocampal sclerosis in 63%, low grade tumors in 26% (ganglioglioma, DNET), cortical dysplasia in 13%, remote infarct, encephalitis, cavernous angioma in 6%. BMI Z scores and BMI percentiles were calculated with SAS Program using the CDC growth charts. 27 children (25%) were obese (BMI > 95% for age) and 22 children (25%) were overweight (BMI % between 85% and 95% for age). The group BMI did not change significantly 2 years after surgery.

Conclusions: Over half the children with temporal lobe epilepsy were overweight or obese persisting after temporal lobectomy. This rate is significantly higher than national survey data (31.6% of children in Ohio are overweight or obese, $p<0.03$, CI 95%, 0.366 to 0.5522). It is also higher than was recently reported in children with new onset epilepsy.

Children with temporal lobe epilepsy maybe at particular risk for obesity. These results need to be replicated with larger cohorts. Early diagnosis and intervention to reduce long term morbidity associated with obesity will be important.

1.197

DO CHILDREN WITH DRAVET SYNDROME HAVE A RECOGNIZABLE FACE?

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Rationale: Dravet syndrome is a severe epilepsy syndrome usually caused by a mutation in the neuronal sodium channel gene SCN1A. Based on personal observations of many children at a large Dravet parents meeting, we had the impression that there may be a specific facial phenotype associated with Dravet syndrome characterized by a small, upturned nose; thin upper lip; smooth, long philtrum; wide-set eyes; and long forehead.

Methods: Families of children with SCN1A-confirmed Dravet syndrome who were members of the International Dravet Syndrome Epilepsy Action League (IDEA League) supplied standard digital photographs of the face of their affected children and unaffected siblings. The photographs were studied in two ways. First, the photographs were compiled into a booklet with cases and siblings randomly mixed. The booklet was sent to a sample of Canadian Pediatric Neurologists who were asked anonymously to identify which children in the booklet were affected by the syndrome and which were siblings. Secondly, the photographs were studied to provide 17 standard measurements that were accurate to <1mm (photogrammetry). To correct for photographic technique and varying magnification, the measurements were analyzed by 16 ratios such as philtrum/face width. Intra-observer reliability was almost perfect.

Results: The booklet included 12 children with Dravet syndrome: 5 males, 7 females, mean age 8.8 years (2.6-16.6 years). There were 12 unaffected siblings: 6 males, 6 females, mean age 9.3 years (4-18 years). The review was by 16 pediatric neurologists. Consensus was defined for each photograph as 10 of 16 pediatric neurologists agreeing if the child was affected or was a sibling. Consensus was achieved in 20 out of 24 cases/siblings (83%). However, when consensus was achieved, only 12 of 20 (60%) were correctly identified as affected or sibling.

For the photographic measurements we chose subjects based on the quality of the images - 13 affected children: 6 males, 7 females, mean age 8.6 years (4-16.7 years) and 10 unaffected siblings included 4 males and 6 females, mean age 11.4 years (6.3-21.8 years). Comparison of the 16 measured ratios of facial features yielded no significant differences between Dravet patients and siblings ($p>0.05$, 2-tailed t-tests).

Conclusions: This study does not demonstrate a specific facial phenotype in Dravet syndrome that can be observed in photographs by pediatric neurologists or identified by standard measurements. The face of children with Dravet syndrome is apparently indistinguishable from their siblings indicating that SCN1A mutations have no dysmorphic effects.

1.198

RETROSPECTIVE ANALYSIS OF PATIENTS WITH NOCTURNAL EPILEPSY

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Rationale: Nocturnal Epilepsy (NE) is a condition that is primarily characterised by seizures exclusively or predominantly during sleep. Although frontal lobe is known to be the main epileptogenic zone and there are familial cases, seizures may arise from other areas with different etiologies. We sought to search for the demographic, aetiological and clinical features of NE for better diagnosis and treatment.

Methods: Patients with NE (e”70% of seizures occur during sleep) who admitted to the university hospital and followed in the epilepsy outpatient clinic between January 1999- December 2010 were included in this study. Patients with idiopathic generalized epilepsy and benign idiopathic partial childhood epilepsies with known relationship to sleep were excluded. All patients underwent physical and neurological examinations, interictal EEG during wakefulness and sleep and MRI. Neuropsychological examination, ictal video EEG recordings and FDG-PET were performed if patients were surgical candidates. The data related to history of febrile seizures (FS), seizure type, EEG and MRI abnormality, therapeutic response and demographic information were analyzed statistically.

Results: Among 910 patients, 90 patients were identified within the age range of 5-84 yrs (mean 31,2 ±14,1) where 54% was female. Mean seizure onset was 13,8 ± 11,8 years. Seizures occur exclusively during sleep in 51% of patients. In 47,1% of patients they were intractable and in 40% well controlled. MRI revealed a structural lesion in 61,2% where majority localized in temporal lobe (TL) with favorable outcome and almost half of them at right the other half, at left hemispheric lateralization. Lesions detected were hippocampal sclerosis (24%), tumour (12%) and cortical dysplasia(10%). Fifty-four % of patients were on monotherapy, the most common drug was carbamazepine ($p<0,001$) and 30 % underwent surgery where 65% had TL epilepsy ($p=0,0014$). History of FS, abnormal EEG, MRI findings and therapeutic response showed no statistical correlation. EEG pathology was more common in TL. Follow-up duration was statistically shorter in refractory group than the others ($p<0,001$).

Conclusions: This study suggested that almost half of the patients with NE were intractable and CBZ was the most common drug in monotherapy. Frontal lobe is less involved than TL where MR was negative in majority of them.

1.199

HEART RATE MAY NOT DIFFERENTIATE EPILEPTIC FROM PSYCHOGENIC NONEPILEPTIC SEIZURES

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Rationale: Ictal and postictal tachycardia have been shown to distinguish complex-partial (CPS) or generalized seizures from psychogenic nonepileptic seizures (PNES). Recent evidence has emerged for autonomic dysfunction in PNES. We reinvestigated pre-ictal, ictal, and post-ictal heart rate (HR) changes in CPS and PNES.

Methods: We screened 205 consecutive elective admissions to the epilepsy monitoring unit (EMU) at our tertiary hospital between January 2008 and 2010 for video EEG confirmed CPS and/or PNES. In cases where multiple seizures were captured in one patient, only the first event of each type was analyzed. PNES was diagnosed, if there was alteration of consciousness and/or bilateral motor elements without epileptiform abnormalities on surface EEG. HR was calculated by an average of three consecutive R-R intervals at 30 sec prior to seizure onset (pre-ictal), maximal HR during the seizure (ictal) and one minute after the seizure (post-ictal) for each event and normalized to the baseline HR of each patient. If determination of HR was obscured by artifacts, this measurement did not go into analysis. Mean, standard deviation (SD) and Student t-tests were performed for each time point to determine differences between CPS and NES. This study was approved by the hospital internal review board.

Results: A total of 44 pre-ictal, 46 ictal, and 44 post-ictal HR measurements in CPS and 41 pre-ictal, 42 post-ictal, and 39 postictal HR measurements in PNES went into the analysis. Mean and SD of the HR for CPS were 104 +/- 20 beats per minute (bpm) pre-ictally, 159 +/- 43 bpm ictally, and 129 +/- 34 bpm post-ictally and for PNES 116 +/- 21 bpm pre-ictally, 157 +/- 37 bpm ictally, and 114 +/- 20 bpm post-ictally. P-values of Student t-tests between CPS and PNES were 0.006 (pre-ictal), 0.493 (ictal) and 0.015 (post-ictal). Comparison of HR pre-ictal vs. ictal and ictal vs. post-ictal within the group of CPS and PNES patients revealed p-values < 0.001 throughout (see Figure 1).

Conclusions: Maximal ictal HR showed tachycardia for both CPS and PNES without significant difference in contrast to prior reports. Compared to CPS, PNES are associated with a greater pre-ictal HR and lower HR post-ictally.

IMAGE: images/908240_A.jpg

Figure 1: Peri-ictal Heart Rate (HR) in % from baseline (* $p < 0.05$, ** $p < 0.01$)

1.200

RECENT UNDERSTANDING IN THE ROLE OF GENETICS IN HOT-WATER EPILEPSY

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Rationale: Hot Water Epilepsy (HWE) a form of reflex or sensory epilepsy wherein seizures are precipitated by an unusual stimulus, the contact of hot water over the head. It is frequently reported from South India. It has complex biological mechanisms that remain largely uncertain. Possible interactions between Genetics and Environmental factors have been hypothesized. We have undertaken a human genetic approach using a whole genome-based analysis to search for genetic loci predisposing to hot water epilepsy.

Methods: Whole genome-wide two-point linkage analysis followed by manual haplotype analysis of a multi-generation family, Family-150 and 227 has been carried out. The family had more than 10 affected members and 14 unaffected members available for the study. We typed over 400 microsatellite markers and carried out parametric linkage analysis using an autosomal dominant mode of inheritance.

Results: First Locus: Genome wide linkage analysis of the first large family provided evidence of linkage for D105412 to chromosome 10q 21. Analysis of five additional smaller HWE families for same marker

on chromosome 10, further strengthened the evidence of linkage to the same chromosomal region with three out of five families showing concordance for the disease haplotype and providing two point LOD score of 4.86 at 60 % penetrance for D105412.The centromere proximal and distal boundaries of the critical genetic interval of about 15Mb at 10q 21.3 - 22.3.

Second Locus : A linkage analysis in a four-generation family manifesting the disorder in an autosomal dominant way demonstrated significant linkage with markers on chromosome 4q24-q28, with the highest two-point LOD score of 3.50 at recombination value (è) of 0 for the marker D4S402. Centromere-proximal and centromere-distal boundaries of this locus were defined by the markers D4S1572 and D4S2277, respectively. The critical genetic interval spans 22.5 cM .

Conclusions: On the basis of this analysis, we conclude that hot water epilepsy is a genetic disorder. Two definite loci over the chromosome 10 and 4 have been identified for the first time in the literature. We are exploring these regions for the causative gene. Preliminary results will be presented.

1.201

IMPROVEMENT OF SEIZURE CLASSIFICATION BY SHOWING A DVD INCLUDING DIFFERENT TYPES OF EPILEPTIC SEIZURES AND NON-EPILEPTIC SEIZURE-LIKE EPISODES TO NON-PROFESSIONAL EYE-WITNESSES - AN UPDATE

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Rationale: The correct and unequivocal classification of episodes with a sudden loss of consciousness (LOC) may be very challenging and difficult. time-consuming and expensive video-EEG-monitoring, extensive cardiologic diagnostics or the implantation of an event recorder are frequently used diagnostic techniques. In single cases we made excellent experiences when showing a DVD including different types of epileptic seizures (ES) and non-epileptic seizure-like episodes (SLE) to observers of the LOC. In this study we systematically addressed the diagnostic value of this approach.

Methods: 20 patients with an unexplained LOC (12 women, 8 men, median age 37 (22-54)), were included in this study. Observers of an event were shown a DVD including different types of ES and SLE. They had to decide which type of seizure on the DVD was most similar to the observed event. The answer was compared to the results of the clinical evaluations including medical history, EEG, and MRI.

Results: In 18 patients video-EEG-monitoring wasn't necessary because observers made a definite classification by means of the DVD which was plausible considering the clinical evaluations (11 syncopes, 5 epilepsies, 2 dissociative seizures). In 2 patients, unconsciousness remained unexplained. In these patients, video-EEG-monitoring revealed epileptic and psychogenic non-epileptic seizures, respectively.

Conclusions: Extended third-party-clinical-history by means of a DVD including different types of ES and SLE improves the classification of unexplained loss of consciousness significantly and may be able to reduce the number of video-EEG-monitorings and event recorder implantations.

1.202

CORRELATION OF HUMAN INTRACRANIAL MICROWIRE RECORDING WITH CLINICAL FACTORS AND OUTCOMES

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Rationale: Intracranial recording from microwires, implanted with clinically required depth electrodes in epilepsy patients, permits observation of single neuron activity in the conscious human brain. Although these microwire electrodes have typically been placed for research purposes, we wondered how the characteristics of the single-unit activity recorded from these microwires might be correlated with clinical characteristics of epilepsy and if the recordings could be used as an additional information for clinical evaluation.

Methods: Toward this end, we examined how the yield of isolated cell activity varies as a function of brain area, the number of days after implantation surgery, and whether the area was determined to be a likely origin of the seizures and subsequently resected. For each pair of implanted microwires, the extracellular voltage was filtered (300-3000 Hz) and 1.15 ms epochs surrounding voltage extrema (> 2.8 s.d. for the channel, 1.15 ms long) were isolated for further analysis. Events for each channel of recording were automatically grouped into clusters of similar waveform shape (G. Celeux, G. Govaert, Computational Statistics and Data Analysis 14, 315, 1992). Each cluster was graded whether it represented isolated single neuron activity on three (0-4) scales: quality of waveform shape, lack of inter-event intervals < 3 ms, lack of power-line frequency harmonics in the event time power spectrum. Using the sum of all three scales, each cluster was classified as either noise (0-3), potential single neuron activity (4-5), or single neuron (SPIKE) activity (e"6).

Results: We examined recordings from 1205 microwires implanted in 14 different cortical areas in 8 patients resulting in 5895 separate clusters of similar waveform shape. 508 clusters of SPIKE activity were identified (average 0.42 SPIKEs/ch). Both the brain area and its subsequent resection had a significant effect ($p=0.0013$) on SPIKE yield (SY). For the four brain areas with the largest number of recordings (hippocampus-H, amygdala-A, entorhinal cortex-EC, and orbitofrontal cortex-OF) considered separately, subsequent resection had a significant effect ($p<0.05$) on SY in 3 areas, increasing yield in H, but decreasing yield in EC and OF. The number of days after implantation surgery had a significant ($p=1e-5$) effect on SY, trending upward toward 0.64 SPIKEs/ch at 7 days post-implantation.

Conclusions: These results show that brain area has the largest effect on SY of factors examined. Subsequent resection status also affected SY and thus SY from microwire recordings may provide additional information regarding the origin of seizures which can be used in clinical evaluation of these epilepsy patients.

1.203

CONTINUOUS VIDEO-EEG MONITORING IN PEDIATRIC INTENSIVE CARE UNITS

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Rationale: Several studies indicate a higher occurrence of seizures in intensive care unit patients, many of which are not clinically apparent. Few of these studies are devoted exclusively to pediatric patients. The purpose of this study is to determine the occurrence of seizures in a cohort of pediatric and neonatal intensive care unit patients.

Methods: Long-term video EEG monitoring studies performed in the pediatric and neonatal intensive care units were reviewed. Age, gender, diagnosis, EEG background, epileptiform activity, time of onset and duration of seizures, presence of clinical or subclinical seizures, and survival were collected.

Results: One hundred thirty-eight recordings encompassing 122 patients were identified. Thirty-four percent of the sessions identified seizures in the first 24 hours: 17% captured electroclinical seizures, 49% were electrographic only, and 34% had both electroclinical and electrographic seizures. Most (70%) of the first seizures occurred within the first hour of recording, but 30% did not. Younger age, epileptiform activity, and periodic discharges were associated with the occurrence of seizures. Diagnoses of head trauma and status epilepticus/recent prior seizure were more likely than other at-risk diagnoses to be associated with seizures; cardiac arrest managed with hypothermia was least likely to be associated with seizures. A quarter of the studies identified non-epileptic events.

Conclusions: Seizures occurred in nearly a third of critically ill pediatric patients undergoing EEG monitoring, and many of these seizures did not have a behavioral correlate. In those at risk for seizures in intensive care units, there should be a low threshold for obtaining long-term monitoring.

1.204

THE FREQUENCY OF PLEDS AS AN ICTAL PATTERN IN NONCONVULSIVE STATUS EPILEPTICUS

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Rationale: Periodic lateralized epileptiform discharges (PLEDs) are a common EEG finding in patients with acute necrotic structural disease such as stroke and herpes encephalitis. It is a persistent rhythmic pattern that can be confused with the rhythmic EEG pattern of nonconvulsive status epilepticus (NCSE). Therefore, we determined the frequency of PLEDs as the associated EEG abnormality in patients diagnosed with NCSE.

Methods: All EEG reports at the University of Virginia from December 1994 to April 2004 were reviewed using full text searching techniques in order to identify a subset where the diagnosis of NCSE was being considered or was diagnosed. This subset of reports was reviewed manually by investigators in order to identify those EEG reports where the diagnosis of NCSE was made, and where the main EEG finding was that of PLEDs. Other EEG, clinical and demographic characteristics were collected.

Results: A total of 18,741 EEG reports were found reviewed. PLEDS were present in 100 EEGs. The diagnosis of NCSE was reported in 76 (0.41%). Of these 76 reports, one report (1.3%) had PLEDs as the main EEG finding. This case was a 52 year old woman who developed altered mental status after having a right hemispheric stroke and subsequent generalized tonic clonic seizure. Right hemispheric PLEDs were seen on EEG. Administration of lorazepam caused resolution of the PLEDs and immediate resolution of her symptoms.

Conclusions: PLEDS are a very rare ictal pattern in NCSE. Additional clinical information should be used to determine whether NCSE is suspected when PLEDS are identified. If NCSE is suspected, PLEDS should be treated as ongoing seizure activity.

1.205

DREAMING EXPERIENCE AS A USEFUL DIAGNOSTIC CLUE FOR SYNCOPAL EPISODES

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Rationale: The differential diagnosis between epileptic seizures and syncopes is a common occurrence in clinical practice. Syncope is often preceded by a symptom complex characterized by lightheadedness, generalized muscle weakness, giddiness, visual blurring, tinnitus and gastrointestinal symptoms. These subjective symptoms are very important in guiding the diagnosis.

After the faint the patients can also report some subjective feelings (e.g.residual weakness, nausea)

The impression of coming out from a dream after the syncopal episode is a subjective symptom commonly reported by patients, if questioned.

The aim of this study is to verify the occurrence of dreaming experience after syncope and after generalized tonic-clonic seizures (GTCS) and its diagnostic value in differential diagnosis.

Methods: We prospectively investigated 100 patients with GTCS and diagnosis of idiopathic generalized epilepsy (Group 1) according to ILAE classification (Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology. Epilepsia 2001; 42: 796-803) and 100 patients with a certain diagnosis of syncope (Group 2) according to Guidelines on Management of Syncope of European Society of Cardiology (The Task Force on Syncope, European Society of Cardiology. Guidelines on Management (Diagnosis and Treatment) of Syncope - Update 2004 - Executive Summary. European Heart Journal 2004; 25: 2054-72): we questioned if they have never felt the impression of coming out of a dream after the loss of consciousness (GTCS or syncope, respectively) in order to verify the incidence of dreaming experience in the two groups.

Results: No differences in demographic characteristics were detected between the two groups: in group 1 there were 38 males and 62 females, in group 2 there were 36 males and 64 females; mean age of patients with epilepsy was 38.6 ± 13.9, of patients with syncope was 40.6 ± 20.9.

In group 1 nobody referred the dreaming experience, whereas in the syncope group 19 patients (19%, 4 males and 15 females) referred this subjective symptom.

Conclusions: Dreaming experience seems to be an additional useful diagnostic clue for syncopal episodes, helping the clinician to differentiate them from seizures. In fact, when present, it can be considered specific for the diagnosis of syncope.

1.206

THE PREVALENCE AND LOCALIZATION OF ITCAL LAUGHTER NOT CAUSED BY HYPOTHALAMIC HAMARTOMAS

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Rationale: Gelastic seizures are characterized by stereotyped episodic unprovoked ictal laughter and are traditionally associated with hypothalamic hamartomas. More recently, ictal laughter originating from other cortical regions has been described. Laughter associated with temporal lobe foci are most often described, however, cases of frontal and parietal ictal laughter are also reported (Pearce, J. Eur Neurol 2004; 52:172-174). It has been suggested that laughter consists of an affective component and a motor component. The affective component involves the temporal basal structures and the motor component the frontal cortex. The true prevalence of extra-hypothalamic ictal laughter and the distribution of cortical regions involved is unknown.

Methods: In an ongoing collaborative effort, children admitted to the epilepsy monitoring units of Dell Children's Comprehensive Epilepsy Center and Cook Children's Comprehensive Epilepsy Center with gelastic seizures as their primary seizure type were reviewed from January of 2010 to May 30, 2010. The localization, underlying pathology and, in cases where surgery was performed, the seizure outcome was explored.

Results: Of 498 admissions, four cases of extra-hypothalamic ictal laughter (0.8%) have been identified. All patients had 3T MRIs to rule out hypothalamic hamartomas and to better define an ictal focus. Three cases had developmental delay and the diagnosis was initially missed in all. The underlying pathology varied greatly. One child had a choroid plexus papilloma with cystic extension into the right occipito temporal region. Another child had hydranencephaly with dysmorphic left frontal and right parietal lobes. A third had a mesial-frontal lesion and the last had primary generalized epilepsy with repetitive diaphragmatic myoclonus causing a laughter-like sound indistinguishable from the ictal laughter heard in the other individuals. Two of 4 patients had epilepsy surgery; both are free of disabling seizures.

Conclusions: In this ongoing analysis, 0.8% of patients presented with extra-hypothalamic ictal laughter as a prominent clinical feature of their epilepsy. It is difficult to localize or lateralize itcal laughter to a specific cortical region as previously described. In children various pathological processes may be involved. Neurophysiology and neuroradiological studies should be done in all presenting cases.

1.207

THE ROLE OF NON-INVASIVE DIAGNOSTIC MODALITIES IN INSULAR/PERIINSULAR EPILEPSY

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Rationale: The insular cortex is a complex structure enclosed in the depth of the Sylvian fissure. Covered by highly functional temporal, frontal and parietal operculae, it can generate a variety of ictal symptoms (e.g. viscerosensory, visceromotor, somatosensory, motor, speech and auditory) falsely leading to a diagnosis of temporal, frontal or parietal lobe seizures. MRI detection of an insular/periinsular lesion facilitates clinical recognition but some cases are MRI-negative. We wished to assess the role of other non-invasive diagnostic modalities in insular/periinsular epilepsy.

Methods: Charts from all patients with insular/periinsular epilepsy seen by one of the authors (DKN) at our epilepsy clinic from August 2002-March 2010 were reviewed. Patients were included if (a) they had seizures related to an epileptogenic insular/periinsular lesion; or (b) had insular seizures/periinsular seizures documented by intrainsular depth electrodes; and (c) had undergone anyone of the following non-invasive tests: video-EEG monitoring, ictal single-photon emission computed tomography (iSPECT), interictal fluorodeoxyglucose-position emission tomography (PET) and magnetic resonance spectroscopy (MRS). Ictal EEG was classified as either localizing (ictal rhythm confined to T3/T4, C3/C4 or P3/P4), lateralizing (to the epileptogenic hemisphere), non-lateralizing (no ictal rhythm or diffuse ictal rhythm), false-localizing (ictal rhythm in the ipsilateral hemisphere other than T3/T4, C3/C4 or P3/P4), a false-lateralizing pattern (ictal rhythm in the contralateral hemisphere). The results of iSPECT and PET were classified as localizing (localize the epileptogenic lobe), lateralizing, non-lateralizing, false-localizing, or false-lateralizing. Results from MRS of the insula were classified as lateralizing, non-lateralizing or false-lateralizing.

Results: Fifty-nine patients were identified as having insular/periinsular epilepsy (including 8 with intracerebral confirmation). Of these patients, 23 had undergone non-invasive diagnostic modalities: EEG (all patients), video-EEG (20/23 patients), MRI (all patients), iSPECT (15/23 patients), PET (12/23 patients) and MRS (4/23 patients). Ictal video-EEG correctly localized the insular/periinsular region of epileptogenicity in 10% and lateralized it an additional 50% of patients. Ictal SPECT correctly localized the insular/periinsular region of epileptogenicity in 27% and lateralized it in an additional 27%. PET correctly localized the insular/periinsular region of epileptogenicity in 25% and lateralized it in an additional 25%. MRS correctly lateralized the insular/periinsular region of epileptogenicity in 25% of patients. Of note, MRI was normal in one patient with depth-recorded insular/periiinsular seizures.

Conclusions: Our results suggest none of the various presurgical evaluations studied here provide consistent localization and at best lateralizes to the correct hemisphere. Although some novel non-invasive techniques are not expected to provide much help (e.g. MEG-EEG and EEG-fMRI), others such as quantitative analysis of MRI are promising and need to be assessed.

1.208

CLINICAL CHARACTERISTICS ACCORDING TO AGE OF ONSET IN PATIENTS WITH TEMPORAL LOBE EPILEPSY: A SINGLE CENTER EXPERIENCE

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Rationale: Temporal lobe epilepsy (TLE), the most frequent localization-related epilepsy, usually starts in childhood or early adolescence. Hippocampal sclerosis (HS) is the most frequently observed pathologic substrate in these patients; however, there are few data on the pathological substrates in TLE of later age onset. We investigated clinical characteristics according to age of onset in patients with TLE.

Methods: We found 409 patients who were diagnosed as having TLE from the Yonsei Epilepsy Registry database. The diagnosis of TLE was based on ictal semiology, EEG, and MRI. The patients was classified into young-age (< 25 years), middle-age (25 to 49), and old-age groups (e"50) according to the age of onset.

Results: Two hundred and twenty-eight patients (55.7%) were men, 269 patients (65.8%) were classified as symptomatic epilepsy and 176 patients (43.0%) were naïve to the antiepileptic drug (AED) treatment at their initial visit. The young-age, middle-age, and old-age groups consisted of 195 (47.7%), 146 (35.7%), 68 (16.6%) patients, respectively. The significant past histories included (permitting duplication) febrile seizure (FS) (n=53), CNS infection (n=45), head trauma (n=22), perinatal problem (n=11), stroke (n=5), brain surgery (n=3), hypoxia (n=2), posterior leukoencephalopathy (n=1). Brain MRI findings were as following: normal (n=159), HS or dual pathology (n=111), atrophic lesion (n=67) (48 with specific etiology), tumorous lesion (n=27), vascular malformation (n=21), malformation of cortical development (n=18), tuberous sclerosis (n=4), miscellaneous (n=2). Mean age of onset was 30.0±18.7 years. Patients with earlier age of onset were more likely to have history of FS, family history of epilepsy (n=26), mental retardation (n=15), and secondarily generalized tonic-clonic seizures (SGTCS). They were also more likely to be under AED treatment at their initial visit and have more frequent self-awareness of complex partial seizures (CPS) (if existed) (27.7±18.6 versus 37.0±18.5; 80.0%, 64.0%, and 56.6% in young-age, middle-age, and old-age groups, respectively). On the analysis of brain MRI findings, HS was more frequently found (40.0%, 18.5%, and 8.8%; $p<0.001$) in young-age group, whereas atrophic lesions being noted less frequently (9.7%, 22.6%, and 22.1%; $p=0.002$). Normal MRI was more frequent in old-age group (34.4%, 38.4%, and 52.9%; $p=0.025$).

Conclusions: This study suggests some differences according to age of onset in clinical characteristics including causes and MRI findings in TLE patients. Higher frequency of normal MRI and untreated status, and lower frequency of SGTCS and patient awareness of CPS in patients with old-age onset may reflect a different epilepsy syndrome from that of childhood onset.

1.209

EMERGENCY PERSONNEL AND PSYCHOGENIC NON EPILEPTIC SEIZURES

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Rationale: People with psychogenic non epileptic seizures (PNES), much like those with epileptic seizures (ES), often present in the emergency room (ER). The recognition and management of PNES in the ER is often problematic. Emergency medical technicians (EMTs) and Emergency Medicine physicians (ERMDs) are usually the first responders and make decisions about initial management. We sought to determine whether these professionals think about the possibility of PNES, have had any training in PNES, and to understand their approach in managing these patients when confronted with patients with acute paroxysmal abnormal behaviors.

Methods: Short questionnaire about PNES and ES were designed and distributed to EMTs and ERMDs (PGY 2 and up) in three busy ERs in New York City. IRB approval was obtained. Questionnaires (anonymous) were collected and descriptive results were tabulated. 43 ERMDs and 105 EMTs responded.

Results: EMTs

35% hand never heard of the diagnosis of PNES. 55% had no formal training about PNES. Of those with PNES training, nearly 50% had learned about it through lectures and their own reading. 83% believed depression /anxiety was a co- condition, while only 13% thought that fibromyalgia was a co-condition. 22% were unsure if they had unknowingly intubated a patient who might have had PNES.

ERMDs

20% had not heard of PNES. 70% had never had formal training about PNES. 28% used IV benzodiazipines to treat PNES in the ER. 56% agreed that Neurologits were best qualified to diagnose PNES, but only 30% would seek Neurological consultation in the ER. 21% believed that malingering was the most common DSM-IV-TR diagnosis in PNES. Less than 50% believed that gradual onset of symptoms was common in PNES.

Conclusions: Despite being the first responders, EMTs and ERMDs had a large knowledge gap in the recognition and understanding regarding PNES. While PNES is a difficult diagnosis to confirm in the ER, it is nonetheless important to consider and recognize, in order to prevent over treatment, and to properly triage these patients for appropriate care. Neurologists need to work with EMT and ERMD specialties to raise awareness and education level with regard to PNES.

1.210

REAPPRAISAL OF EPILEPSY IN PATIENTS WITH DOWN SYNDROME

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Rationale: In Down syndrome(DS), a clear relationship between age and type of seizures or epilepsy is known. A bimodal distribution of epilepsy, with early onset (<1y) and late onset (>30y) was also noted by Pueschel et al. in 1991. Now that life expectancy of patients with DS becomes longer, it is clinically relevant to reappraise the characteristics of epilepsy with Down syndrome in relation to age.

Methods: We retrospectively investigated 22 patients (male 16, female 6) with DS and epilepsy based upon their medical records. Evaluated were the distribution of age at seizure onset, patients' demographics, characteristics of seizures, types of epilepsy, electroencephalographic findings, treatment, and course of the disease.

Results: As age at onset of epilepsy showed triphasic distribution, we divided our subjects into three groups; infant onset, juvenile onset, and presenile onset group.

"Infant onset" group consists of 8 patients, whose age at onset ranged from 2 month to 18 month. Seizures of this group were exclusively epileptic spasms with head nodding. In 6 patients, spasms in clusters were described, and 5 patients were diagnosed as West syndrome and treated by ACTH therapy and/or antiepileptic medication. Response to these treatments varied from complete cessation to persistence into later life.

"Juvenile onset" group consists of 11 patients, whose age at onset ranged from 10 years to 24 years. Although most of patients in this group had multiple seizure types, the commonest was astatic seizure which was complicated with various motor components described as tonic, clonic, jerky, versive, or rotatory. Intractability to medication was

marked. Furthermore, 3 of 11 patients entailed elements of reflex epilepsy. Their triggering factors were touching hot water by foot, stumbling, or unexpected loud sound.

"Presenile onset" group consists of 3 patients whose age at onset ranged from 41 years to 56 years. Seizure type of 3 patients in this group was generalized tonic-clonic seizure. In the course of disorder, 2 of 3 patients progressively show marked myoclonus on awakening. Around the onset of epilepsy, progressive deterioration of cognition and behavior along with gait disturbance were noticed. Significant diffuse cerebral atrophy with marked enlargement of ventricles was already evident on MRI/CT scan even at the onset of epilepsy. Seizures were refractory to medication.

Conclusions: Types of seizures and epilepsy were uniform in each group of infant onset and presenile onset, while elusive and various forms of seizures including reflex pathology were recognized in juvenile onset group. Progressive deterioration of cognition and motor function was seen in epilepsy of presenile onset. It may be clinically significant to provide the patients with DS and their families with appropriate treatment and perspectives based on these characteristics of epilepsy.

1.211

PECULIAR SEIZURES IN THE INFANTILE EPILEPSY WITH CDKL5 (CYCLIN-DEPENDENT KINASE-LIKE 5) MUTATION/ DELETION

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Rationale: To clarify characteristics of seizures in infants with CDKL5 mutation/deletion for early diagnosis.

Methods: We investigated ictal video-EEG in 4 infants with CDKL-5 (cyclin-dependent kinase-like 5) mutation/deletion; 1 boy with single base missense mutation, 2 girls with single base deletion with frameshift, 1 girl with microdeletion. We performed and analyzed video-EEG monitoring between 3-30 months of age.

Results: Epilepsy started between 2-7 weeks of age in all. Common characteristics of recorded seizures stared with bawling, followed by gestural automatism or head/eye deviation, then tonic posturing for 10 seconds accompanied with marked slowing or attenuation on EEG, thereafter mild rhythmic (2Hz) jerking of extremities, finally evolved to epileptic spasms in a series of short intervals (3-4 sec). Interictal EEG showed no abnormal findings at the onset of epilepsy, but hypsarrhythmia or diffuse spike and waves between 6-18 months.

Conclusions: Infants with CDKL5 mutation/deletion are reported to have epileptic spasms in a series, generalized tonic clonic seizures, or migrating focal clonic seizures. The present study revealed that epilepsy with CDKL5 mutation/deletion started with peculiar combined seizures instead of just simple epileptic spasms or GTC in infancy. Normal interictal EEG at the onset of epilepsy and ictal EEG findings with marked slowing or attenuation also would be useful diagnostic clues to CDKL5 mutation/deletion.

1.212

IATROGENIC SEIZURES IN PATIENTS WITH INTRACRANIAL EEG MONITORING

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Rationale: Anti-epileptic medication therapy is not always sufficient to manage seizures. In an appropriately selected person, surgery can be an effective treatment option. Intracranial EEG monitoring is considered the gold-standard for seizure localization. The risks associated with intracranial EEG monitoring, primarily subdural grids have been documented. It has been observed that intracranial monitoring can be associated with subclinical cerebral edema which has presumably led to falsely localizing seizures. However, little is written regarding false localization associated with intracranial EEG monitoring.

Methods: We undertook a retrospective review of all patients admitted to the Mayo Clinic Arizona Epilepsy Monitoring Unit (EMU) from January 2005 to May 2010. Patients who were included in the study were those who had any type of intracranial monitoring and magnetic resonance imaging (MRI)with intracranial electrodes in place. Those patient's MRI reports were then reviewed for findings of cerebral edema associated with intracranial electrodes.

Results: : In the period of time reviewed, there were 50 admissions to the EMU for intracranial monitoring and 32 of those had an MRI obtained with intracranial electrodes in place. These 32 monitoring events occurred in 27 individual patients. No cases of edema were noted in patients with subdural electrodes. Six patients had subclinical cerebral edema surrounding temporal depth electrodes, representing 25% of patients with depth electrodes during the study period. In 3/6 subjects electrographic seizures without clinical manifestation were recorded from the depth electrode with surrounding edema that were distinct from typical clinical seizures and appeared to be iatrogenic. Subject 1 had typical seizures arising in the right mesial temporal lobe with subclinical seizures arising in the left temporal neocortex with left sided edema on MRI; seizure free at 8 months after right temporal lobectomy. Subject 2 had typical seizures arising in right mesial temporal lobe and subclinical seizures arising right temporal neocortical; seizure free 15 months after selective right amygdalohippocampectomy. Subject 3 had typical seizures arising right mesial temporal and inferior frontal with subclinical seizures arising left mesial temporal; with plan for more extensive right temporal and frontal intracranial implant. There were no cases of similarly discordant subclinical seizures with depth electrodes in the absence of cerebral edema on MRI. One individual had falsely localizing clinical seizures as well as PLEDs associated with a subdural grid, yet ultimately became seizure free.

Conclusions: Iatrogenic, falsely localizing, subclinical, seizures were seen in 8% of patients undergoing intracranial EEG monitoring, primarily with temporal depth electrodes associated with subclinical cerebral edema on MRI. This is a concerning complication of intracranial EEG monitoring as this finding on EEG might lead epileptologists to disregard these patients as candidates for epilepsy surgery. In fact the patients in our study have done well post-operatively.

1.213

"PERIICTAL BED LEAVING" IN TEMPORAL LOBE EPILEPSY: INCIDENCE AND LATERALIZING VALUE

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Rationale: The main purpose of our study was to establish the incidence and lateralizing value of "periictal bed leaving" (PBL) in patients suffering from temporal lobe epilepsy (TLE).

Methods: We reviewed a total of 97 patients (59 men and 38 women). All patients underwent a successful epilepsy surgery procedure and were classified as Engel I at the 2-year follow-up visit. Histopathological examination revealed hippocampal sclerosis (TLE-HS) in 60 patients and other lesions in 34 patients (TLE-oth); 3 patients had no lesions.

We reviewed 380 seizures (234 seizures in patients with TLE-HS and 146 seizures in patients with TLE-oth). Of those, 202 seizures arose from the right temporal lobe and 178 from the left temporal lobe.

PBL was defined as lateralized leaving of the bed occurring during the seizure or up to 3 minutes after the end of the seizure.

Fisher's exact test was used for the statistical evaluation of categorical variables. A P value < 0.05 was considered as statistically significant.

Results: PBL was observed in 27 out of 97 patients (27.8%), in 44 out of 380 seizures (11.6%). PBL was more frequently present in patients with TLE-HS than in those with TLE-oth (33% vs.18.9%; p=0.095). In total, PBL ipsilateral to the seizure onset zone was observed in 62.9% of patients and 68.2% seizures (p=0.102 and 0.043). In patients with TLE-HS, PLB was present ipsilateral to the seizure onset in 80% of patients and 83.2% seizures (p=0.006 and 0.002). Similarly, in patients with TLE-oth, PLB was present ipsilateral to the seizure onset in 14.3% of patients and 35.7% seizures (p=0.577 and 0.413). There were no differences in the incidence and lateralizing value between patients with left-sided TLE and those with right-sided TLE.

Conclusions: PBL is a relatively frequent periictal sign in patients with TLE. In patients with TLE-HS, the side of PBL lateralizes the seizure onset zone to the ipsilateral temporal lobe.

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1.214

AN EPILEPSY FELLOW'S PERSPECTIVE ON THE DISCREPANCY BETWEEN EXPOSURE TO A PATIENT POPULATION AND CONCOMITANT CLINICAL EDUCATION

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Rationale: Most epilepsy fellowship training programs in the country are structured to teach about the diagnosis, evaluation, and treatment of epileptic seizures (ES). However, epilepsy fellows frequently encounter patients with psychogenic non-epileptic seizures (PNES). The incidence of PNES is probably significantly higher than most clinicians realize and approximated to be 5% of the incidence of epilepsy. Previous studies have suggested that the incidence of PNES is 5-20% in an outpatient epilepsy population, and an incidence of up to 45% for inpatients studied at epilepsy monitoring centers. Therefore, education on PNES should be an important part of clinical epilepsy training. We reviewed our epilepsy monitoring database in order to determine what percent of patients presenting to our Epilepsy Monitoring Unit (EMU) were ultimately diagnosed with PNES during their stay, as encountered by an epilepsy fellow during the first year of training.

Methods: We retrospectively reviewed the medical records for all patients admitted to our EMU for scalp-electrode video-EEG monitoring from 6/17/2009 to 6/10/2010 at the Barrow Neurological Institute in order to identify the prevalence of different seizure types. Patients were categorized into four main groups based on their diagnosis according to their ictal and interictal EEG findings, event semiology, and imaging studies: generalized seizures, partial seizures, psychogenic non-epileptic seizures (PNES), or other paroxysmal physiological disorders (i.e. syncope).

Results: A total of 293 patients underwent continuous video-EEG monitoring with scalp electrodes between 6/17/2009 - 6/10/2010 and were evaluated by a single fellow. Of those patients, 27 (9.2%) had generalized onset seizures, 79 (27%) had partial onset seizures, and 93 (31.7%) had PNES. In addition, 12 (4.1%) had both true ES (generalized or partial onset) and PNES during the monitoring. Of the remaining patients, 10 patients had no events but interictal findings consistent with ES (generalized onset or partial onset seizures), 6 had probable simple-partial seizures without EEG changes, 3 had an undetermined seizure type, and 20 (6.8%) patients had other paroxysmal physiological events (7 cardiogenic, 5 panic attacks, 4 parasomnias, and 4 had other causes). 43 patients (14.7%) had no events and no interictal findings. Overall, we identified a total of 105 patients (35.8%) with PNES (with or without concurrent ES), compared with 125 patients (42.7%) with epilepsy alone based on ictal and interictal findings.

Conclusions: Considering the fact that PNES patients accounted for more than one third of the EMU patients encountered by our epilepsy fellow during a one year period of time, education toward the diagnosis and treatment of PNES should be an essential component of epilepsy fellowship training programs, which may lead to earlier diagnosis and more effective treatment for patients with psychogenic non epileptic seizures.

1.215

ELEVATION OF SERUM PROLACTIN LEVELS IN DIFFERENT SEIZURE CHARACTERS

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Rationale: Rising in serum prolactin (PRL) has never been studied in relation to different characters of seizures under video-EEG monitoring. This study aims to assess the correlation between post-ictal PRL levels and seizure details namely semiology, duration of seizure, seizure-free interval and site of epileptogenic zone.

Methods: Serum PRL levels were measured in 89 seizures (all were focal seizures with 24 secondary GTCs and 44 auras) from 55 patients (30 females, 25 males) with medically intractable epilepsy who

underwent long-term video-EEG monitoring. Blood samples were collected at 30 minutes, 1 hour, and 6 hours after seizures. A 6-hour PRL level was used as baseline for each seizure. PRL levels more than 2 folds above baseline were considered as elevation. Seizure details were analyzed from video-EEG recordings and correlated with PRL levels.

Results: Logistic regression analysis revealed significant increase of PRL in seizures with aura (p=0.018, OR(95%CI); 3.11(1.22-7.96) at 30 minutes; p=0.027, OR(95%CI); 2.63(1.11-6.22) at 1 hour post-ictally), GTC (p=0.015, OR(95%CI); 6.60(1.44-30.30) at 30 minutes; p=0.027, OR(95%CI); 2.95(1.13-7.67) at 1 hour post-ictally), tonic seizures (p=0.013, OR(95%CI); 2.90(1.25-6.71) at 1 hour post-ictally), seizures with post-ictal confusion (p=0.013, OR(95%CI); 0.30(0.11-0.77) at 30 minutes post-ictally), EEG duration (p=0.025, OR(95%CI); 2.57(1.12-5.87) at 30 minutes post-ictally) and in females compared to males (p=0.006, OR(95%CI); 0.18(0.05-0.61) at 30 minutes; p=0.018, OR(95%CI); 0.26(0.08-0.79) at 1 hour post-ictally). Most correlations were stronger at 30 minutes than at 1 hour after seizures. Multiple logistic regression analysis revealed that only aura had significant correlation with elevated serum PRL at 30 minutes after seizures (p=0.005, OR(95%CI); 11.24 (2.08-60.69)). No correlation was found between elevated PRL and the following seizure characters: eye deviation, version, dystonic posturing, clonic seizure, automatism, impaired consciousness, clinical duration, seizure-free interval or the site of epileptogenic zone.

Conclusions: Our findings suggested that elevation of post-ictal serum PRL was related to seizures with long duration and female gender.

1.216

PREDICTION OF GENERALIZED TONIC-CLONIC SEIZURES DURING AND WITHIN THREE DAYS AFTER INPATIENT EPILEPSY MONITORING

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Rationale: The risk of generalized tonic-clonic seizures (GTCs)is relevant to the safety of patients during epilepsy monitoring, during which drugs are often reduced.

High risk may extend into the early post-discharge period, before full medical control is re-established. We searched for factors predicting GTC occurrence during these times.

Methods: We conducted a chart analysis and phone interview of 100 patients from two cohorts of 50 consecutive patients admitted to the University of Alabama Hospital seizure monitoring unit who met criteria: 1) history of GTCs before admission or observed GTCs during monitoring 2)able to provide a history of events during the 72 hours after discharge and 3) no psychogenic seizures during monitoring. Data on suspected preadmission seizure types, inhospital seizures, medication reductions, time from last inhospital GTC to discharge, time from medication restart to discharge, and use or nonuse of short-term lorazepam (LZP) were collected. Patients were surveyed by telephone to determine seizure occurrences, emergency visits, and rehospitalizations within the 72 hours after discharge.

Results: 442 patients were admitted during the period of observation. Of the 98 patients who had a history of GTCs before admission, 55 (56%)had at least one GTC inhospital. In comparison, only 2 of 344 patients admitted during this time without a history of GTC had a documented GTC inhospital (p <0.001). 107 of these 344 had observed psychogenic events. Two of the 100 patients in the study had an early posthospital GTC- within 3 days after discharge, though 11 others had complex partial and 2 others simple partial seizures during these 72 hours. 7 of 46 receiving LZP (usually 1 mg TID for 3 days) had early posthospital seizures vs. 8 of 54 who did not (NS). The mean length of stay for the 100 patients in the study, none of whom had psychogenic seizures, was 3.3 days. No evidence of premature discharge was found among those with early posthospital seizures.

Conclusions: Patients who have a history of GTCs are at very high risk for GTCs during seizure monitoring, and should be watched carefully. Those without such a history are unlikely to have a GTC precipitated. However, we recognize that some patients with a history of GTCs may be found to have GTC-like psychogenic events. Ideally, patients with any GTC history should be under direct observation by staff or family during monitoring. A brief course of LZP made no difference in the rate of early posthospital seizures, though doses used were low.

1.217

TO LAUGH OR NOT TO LAUGH: DICHOTOMY FAVORING RIGHT TEMPORAL LOBE ONSET OF SEIZURE

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Rationale: Ictal EEG recordings (Biraben A, Sartori E, Taussig D Epileptic Disord 1999;1:221-228; Dericioglu N, Cataltepe O, Tezel GG, Saygi S Epileptic Disord 2005;7:1137-141), brain stimulation (Padberg F, Juckel G et al. J Neuropsychiatry Clin Neurosci 2001;13:206-212) and focal brain lesions (Takahashi T, Yucel M et al. Prog Neuropsychopharmacol Biol Neuropsychopharmacol 2010;34:98-103) support the concept of laterality of emotive function.

As an epileptic manifestion, laughter most commonly occurs in children who have hypothalamic hamartoma. Among adults, gelastic seizures take origin from other limbic structures, including temporal lobes (Gascon GG and Lombroso CT Epilepsia 1971;12:63-76), cingulate gyrus (Sperli F, Spinelli L, Pollo C, Seeck M Epilepsia 2006;47:440-443), and frontal lobes.

Previous citations of gelastic seizures have not suggested a predictable laterality of seizure onset. We performed a review of our patients with gelastic seizures to examine this issue.

Methods: We performed a retrospective chart review of adult patients at our institution who reported a gelastic component to their seizure semiologies. We reviewed case histories, brain imaging, interictal EEG, and results of VEEG monitoring. This study was done with the approval of the Institutional Review Board at the Medical University of South Carolina.

Results: We identified a cohort of 19 patients who reported gelastic seizures. Fifteen underwent VEEG monitoring which captured their seizures. Three of this group had seizures which arose independently in right and left temporal lobes, the results of which are the subject of this report. These three cases with bilateral seizure onset included 2 women and one man. Data concerning seizure etiology are summarized in Table 1.

Twenty-three seizures were recorded among these three patients, including 8 events of right temporal onset, 12 with left temporal onset, and 3 events for which laterality was unclear (Table 2). Half of the seizures with right temporal onset were gelastic, versus none of those of left temporal onset and none of those of indeterminate laterality.

Conclusions: Among three patients with complex partial seizures of independent, bilateral temporal lobe onset, gelastic features occurred exclusively with events of right temporal lobe onset. This finding appears to confirm the concept of the cerebral laterality of emotive function.

Table 1: Seizure etiology

IMAGE: tables/879439_T1.jpg

Table 2: Ictal EEG

IMAGE: tables/879439_T2.jpg

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UNILATERAL ABDOMINAL WALL CLONIC ONSET SEIZURES (AWCSS)

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Rationale: To review the local experience of patients with AWCSs.

Methods: A retrospective review of 540 consecutive video-EEG telemetry admissions.

Results: 2 patients with AWCS were identified.

Patient #1. A 41 year old female with normal intelligence and examination has had seizures since age 12 years. Seizures are exclusively nocturnal (frequency = 4/month). The seizures awaken her from sleep with jerking movements of the left abdominal wall (below the costal margin and above the iliac crest); after 30-45 seconds clonic abduction movements of the left shoulder begin and persist for 1-2 minutes followed by “numbness” of the left face, arm, and leg lasting 1-2 minutes. Habitual seizures were captured during video-EEG telemetry with 1 (on reduced antiepileptic drug) progressing to a secondarily generalized tonic-clonic seizure. The interictal EEG was normal, and the ictal EEG was uninterpretable secondary to movement artifact. The MRI was normal.

Patient #2. A 34 year old male with right primary sensory cortex seizures since age 25 years of unknown etiology. Investigations included intracranial subdural electrodes (a 20 contact grid over the central region and 6 multicontact strip electrodes covering adjacent parietal-frontal cortex). Following the subdural electrode placement the patient had, in addition to his habitual seizures, multiple ictal events completely dissimilar to anything previously experienced. These seizures consisted of left abdominal wall clonic contractions (frequency approximately 2 Hz) lasting 2-3 minutes. These clinical events were associated with electrographic seizure rhythms maximal at 2 electrodes located over the right superior paracentral lobule.

Conclusions: AWCSs are rare. Only 4 patients with isolated AWCSs have been previously reported (plus 6 patients with epilepsia partialis continua). We report the clinical details of 2 patients with AWCSs including the first documented with intracranial EEG monitoring. AWCSs originate in the contralateral high sensorimotor convexity.

1.219

NEW EVIDENCE OF HETEROGENEOUS ETIOLOGY AND OUTCOME OF PRES AMONG PATIENTS WITH SOLID ORGAN TRANSPLANT

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Rationale: Posterior reversible encephalopathy syndrome (PRES) is a common cause for seizures in post-transplant patients. The anti-rejection agents cyclosporine and tacrolimus are most strongly associated with this syndrome. This syndrome is usually considered to be fully reversible and not a cause of chronic epilepsy or persisting cortical dysfunction. Recently, greater heterogeneity of etiology and outcome of PRES has been postulated. To further evaluate the range of features of PRES, we retrospectively evaluated radiological and clinical characteristics of PRES in patients with different solid organ transplants in a single transplant center.

Methods: We searched the database of the University of Minnesota Transplant Information Services (TIS). We searched for patients with seizures, encephalopathy and MRI. We reviewed the electronic medical records of such patients to find evidence of PRES. Among patients with PRES, we reviewed MR images, and extracted information on seizures, neurological condition and medication at the time of the PRES and clinical outcome.

Results: Among 390 patients with solid organ transplants, we found 15 patients with PRES. All patients had posterior cerebral white matter edema on MRI, but many also had frontal and temporal lobe changes. Follow up MRI (averaging 7 months from acute MRI) showed complete resolution of edema in 7 patients, partial resolution in 3, a persisting lesion (parietal cortical encephalomalacia) in 1, and recurrent PRES in 1; 3 patients died or were lost to follow up. New (after PRES) neurological dysfunctions in 3 patients included hemiparesis, partial epilepsy, and mild cognitive impairment. Before the onset of PRES, 2 patients had only used mycophenolate for immunosuppression, 1 used only tacrolimus, and the others were on combinations of mycophenolate with cyclosporine or tacrolimus.

Conclusions: This is the first series of PRES to find the syndrome in association with mycophenolate used as the sole immunosuppressive/anti-rejection agent. In agreement with findings of other recent series, we observed patients who sustained persisting cortical dysfunction or lesions, contradicting the putative full resolution of PRES.

Acknowledgments: This study was supported by the University of Minnesota Comprehensive Epilepsy Center research fund.

1.220

TITLE- INTERICTAL SPIKES AND HEART RATE VARIABILITY

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Rationale: Rationale-Sudden unexpected death in epilepsy (SUDEP) affects 0.35 cases/1,000 person-years and is the most common epilepsy-related cause of death. As far as we know, there is no single risk factor common to all SUDEP, suggesting multiple mechanisms. Animal studies indicate that interictal discharges can affect the cardiac rate but this is not fully established in humans. If human interictal spikes are proven to affect heart rate variability, this may in turn provide further insight into the underlying mechanism in SUDEP.

Methods: Methods-We reviewed 15 consecutive EEG's of adult patients with focal spike discharges (IEDs) electively admitted for prolonged video EEG monitoring from May 2008 to May 2010 using Nihon Kohden recording systems. Patients with known cardiac or pulmonary problems, or taking medications which control heart rate, were excluded. Patients with generalized epilepsy or below 18 years were also excluded. We looked at 20 epileptiform focal single spikes per patient and measured the RR intervals 4 seconds before, during, and 4 seconds after and compared them to the RR intervals similarly obtained in a control group. The control epoch always ended or began within 10 seconds before or after, respectively, the interictal spike epoch. This helped to select interictal and control epochs occurring in similar states.

Results: RR intervals corresponding to the Interictal spike waves were found to be longer than the control group (p value=0.01), and heart rate variation before and after spikes was greater than in controls. These findings were not spike localization dependent.

Conclusions: Conclusions- Interictal epileptiform activity is associated with heart rate variability. Although it is possible that an independent mechanism produces both the RR variability and interictal spikes, we believe RR variability results from direct cortical neural stimulation.

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CLINICAL FINDINGS IN HOSPITALIZED PEDIATRIC PATIENTS WITH STATUS EPILEPTICUS

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Rationale: To describe clinical features and identify predictors of status epilepticus (SE) in hospitalized children admitted with seizures.

Methods: The inpatient database for 2008 at our institution was reviewed for patients with epilepsy and seizures. Patients with and without history of SE were compared. We defined SE as seizures lasting e" 5 minutes or recurrent seizures without regaining consciousness between two consecutive seizures for e" 30 minutes.

Results: 425 patients (51% male) were identified. Median age of seizure onset was 25 months (0.03-288 months). Median number of semiological seizure types was 2 per patient (1-4).

The SE group included 155 patients (36.5% of total; 57% male). These had a previous history of status or new presentation of SE in 2008. Among these, 141 (91%) patients had a history of SE prior to admission and 14 (9%) had no history of seizures presenting with new onset SE. Amongst the 141 patients with history of SE, 80 (56.7%) were admitted in 2008 due to SE, and 61 (43.2%) had a history of SE before 2008.

The NON-SE group included 270 patients (63.5% of total; 47.4% male). These did not have SE in the past or during admission. 240 (88.9%) had a history of seizures prior to admission, and 30 presented with new onset seizures on admission in 2008.

The median age of seizure onset in both groups was similar (25 months; non-significant). Patients in the SE group presented more often with multiple seizure types (SE 103/155, 66.4%; NON-SE 143/270, 53%; P<0.01). 51 (32.9%) SE patients and 128 (47.4%) NON-SE patients had only one seizure type. 71 (45.8%) SE patients and 96 (35.5%) NON-SE patients experienced two seizure types, and three or more seizure types were identified in 33 (21.2%) SE and 46 (17%) NON-SE patients.

SE group patients were prescribed more antiepileptic drugs (AEDs) prior to admission (median 2, range 0-6) than NON-SE patients (median 1, range 0-7; $p<0.001$). SE group patients also were more likely to have been hospitalized in the past (94; 60.6 %) than NON-SE patients (97; 35.9%; $p<0.001$).

Prior to admission, EEG was available in 396 patients. Spikes were more common in EEGs of SE patients (127/135, 94.1%) than in NON-SE patients (216/261; 82.8%; $p<0.01$). SE patients also had more frequent slowing on EEG (38/135; 24.5%) than NON-SE (48/261; 18.3%; $p<0.05$).

Amongst 155 SE patients, 134 brain MRIs were available. In the NON-SE group, 244 out of 270 patients had an MRI. Patients with a history of SE more frequently had an abnormal MRI (80; 59.7%) than NON-SE patients (107; 53.7%; $p<0.05$).

Conclusions: Pediatric in-patients with history of SE are more likely to experience multiple seizure types, receive treatment with more AEDs, have more frequent hospital admissions, and are more likely to have an abnormal EEG and brain MRI than patients who do not have a history of SE. Findings need to be interpreted in the context of data acquisition. Each of these differences may contribute to predicting the likelihood of SE in an individual with epilepsy.

1.222

RETROSPECTIVE STUDY IN CHARACTERIZATION OF NON-EPILEPTIC EVENTS IN PATIENT WITH SOME DEGREE OF DEVELOPMENTAL DELAY- INTELLECTUAL DELAY

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Rationale: Non-Epileptic events (NEE) in patients with developmental delay/ intellectual disability (DD/ID) represent a considerable challenge. Our goal is to determine whether we can identify factors that can prospectively aide clinical identification of NEE in the DD/ID population. This study represents our initial results on the etiology of NEE in patients who are typically developing (TD) compared to those with DD/ID.

Methods: A retrospective review of data in 2009 at the Pediatric Epilepsy Monitoring Unit (PEMU) at our institution. For all patients, the admitting diagnosis was spells of unknown origin. The referring physician's clinical history was reviewed. Episodes were classified as either epileptic seizures (ES), behavioral/psychogenic non-epileptic events (PNEE) or physiologic non-epileptic events (PhysNEE). The clinical characteristics and semiology of the NEE were compared in TD vs DD/ID patients

Results: Of the 348 patients admitted to the PEMU, 165(47%) were admitted secondary to a diagnosis of unknown origin. NEE was confirmed in 93 (56.3%) patients. 44 were females (47.3%), age range was 1month - 19 years, (mean 8.4 years).

Of the 93 confirmed NEE patients, 31 (33.3%) had physiologic etiology and 64 (66.7%) had behavioral/psychogenic etiology. 2 patients (2.1%) had events with both etiologies. Comparing the 2 groups, in the 58 (62.4%) TD patients, the diagnosis of NEE consisted of: 20 (34.4) physiologic NEE, 39 (67.2%) behavioral/psychogenic NEE, and 1 both. In the 35 (37.6%) patients with DD/ID, the diagnosis of NEE consisted of: 11 (31.4%) physiologic NEE, 25 (71.4%) behavioral/psychogenic NEE and 1 had both.

40 patients with NEE (43%) had a concurrent diagnosis of epilepsy. Comparing the 2 groups, 21 (36.2%) TD patients had epilepsy vs. 19 (54.2 %) with DD/ID. Of the 21 TD patients with epilepsy, 17 (81%) had PNEE and 4 (19%) had PhysNEE. Of the 19 patients with epilepsy and DD/ID, 16 (84.2%) had PNEE and 3 (15.8%) had PhysNEE.

Of the 53 (57%) NEE patients without epilepsy, 37 (63.7%) with NCF did not have epilepsy vs. 16 (45.7%) with DD/CI. In the 37 TD patients w/o epilepsy, 22 (59%) had PNEE and 15 (41%) had PhysNEE compared to 16 patients with DD/ID w/o epilepsy in whom 9/16 (56%) had PNEE and 7/16 (44%) had PhysNEE

Conclusions: Caregivers and physicians, have difficulty distinguishing NEE in patients with DD/ID. In both TD and DD/ID patients, the majority of NEE is secondary to behavioral/psychogenic causes, and in children with comorbid epilepsy, there is an even higher proportion of NEE secondary to PNEE. Therefore, etiology alone does not distinguish the two groups, and other guidelines will be needed to aid the recognition of NEE in DD/ID patients.

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EEG CHARACTERISTICS IN PYRIDOXAL 5'-PHOSPHATE DEPENDENT EPILEPSY

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Rationale: Pyridoxal 5'-phosphate (PLP) dependent epilepsy is a relatively newly recognized disorder which is diagnosed by cerebrospinal fluid (CSF) analysis and gene testing. However, the electroencephalographic (EEG) patterns that could potentially raise the index of suspicion of this syndrome have not been characterized to date. Here we report EEG findings of two such patients.

Methods: Patients were included, if they had seizures refractory to antiepileptic drugs, decreased PLP levels in CSF, and became seizure free after taking PLP. Pyridoxamine 5'-phosphate oxidase (PNPO) gene sequencing, performed on one patient, confirmed the presence of a mutation in that gene. EEGs performed before starting PLP were reviewed and a retrospective chart review was done.

Results: Case 1: A 3 year old African American boy who had, as of the age of 2 years, recurrent complex partial seizures that occurred up to four per day and were refractory to levetiracetam, carbamazepine and pregabalin. EEG at age 3 revealed, interictally, a background that achieved 8Hz with frequent, bilateral independent, C3, C4, T3, and T4 spikes, more on the left, in wakefulness as well as continuous 2-2.5Hz generalized spike and slow wave of higher amplitude over C3 and C4 in sleep (consistent with electrical status epilepticus in sleep) and ictally, runs of left hemisphere spike slow wave discharges, predominantly C3 and T3, usually for 5-15 seconds.

Case 2: A 2 month old Hispanic boy who had neonatal status epilepticus at the age of 10 hours and subsequent recurrent generalized tonic-clonic seizures (2-8/day) over the next several weeks. His seizures were refractory to phenobarbital, fosphenytoin and lorazepam. When first seen by us, EEG on day 18 of life revealed bilateral, independent paroxysmal multifocal sharp waves, mostly over T4 interictally. These discharges often occurred in runs lasting from a few seconds to few minutes. There was also excessive discontinuity of the background.

Conclusions: We observed the following pre-treatment EEG manifestations of PLP dependent epilepsy: 1) Interictally: frequent, multifocal, independent spike or sharp wave discharges, 2) Interictally and ictally: runs of unilateral and repetitive spikes/slow waves, and 3) Electrical status epilepticus in sleep. These EEG findings, in the appropriate clinical setup, should raise the suspicion of PLP dependent epilepsy.

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CATASTROPHIC EPILEPSIES SEEN IN THE NEONATAL PERIOD IN JAPAN

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Rationale: Catastrophic epilepsies (CE) are age-related epileptic syndromes characterized by a variety of behavioral seizure manifestations, distinctive electroencephalogram (EEG) patterns, and poor outcomes that often start in the neonatal period. As seizures in the newborn have generally been identified only by direct clinical observation, there is usually a lack of objectivity whether seizures are categorized as epilepsies or non-epilepsies.

Methods: A major characteristic of neonatal seizures is electro-clinical dissociation and some electro-graphic seizures do not produce clinical symptoms. It is difficult to correctly identify real epilepsies or epileptic syndromes in the neonatal period without ictal EEG. Some epileptic syndromes starting in the neonatal period such as early myoclonic encephalopathy (EME), Ohtahara syndrome (OS), or migrating partial seizures in infancy (MPSI), are categorized as CE. A suppression-burst EEG pattern (SBP) is usually seen in neonates with serious brain damage or neonatal epileptic syndromes.

Results: We will highlight our recent experience of CE in Japan and also propose a precise definition for SBP which has not correctly been identified in the literatures. We experienced 3 cases of OS, 2 cases of EME and a case of MPSI in this 7 yeras. We propose the tentative definition of SBP in OS as follows. The bursts must consist with high amplitude non-synchronized paroxysms like hypsarrhythmia and continue for 2 to 6 seconds. The suppression (low-amplitude) phase must show less than 10 ìV or flat tracing and continues for 3 to 5 seconds. Suppression and burst phases must appear alternately and regularly every more than five seconds. SBP should be seen in both during sleep and awake states and should not change according to sleep-wake cycle.

Conclusions: Epileptic encephalopathies with SBP in neonatal period are known to evolve into relatively few types of epileptic syndromes. We will emphasize the importance of ictal EEGs for diagnosis and treatment of neonatal epilepsies and epileptic syndromes. The SBP in OS should be distinguished from SBP in EME.

1.225

EPILEPTIC LOSS OF CONSCIOUSNESS INVESTIGATED BY PROSPECTIVE BEHAVIORAL TESTS

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Rationale: Rationale: Loss of consciousness in epileptic seizures can cause substantial issues such as social stigma, physical injuries, and car accidents. However, the underlying mechanisms involved in the loss of consciousness are poorly understood because directly evaluating consciousness during randomly occurring and brief epileptic seizures is technically difficult. Previous studies have been limited by the lack of standardized behavioral testing batteries to assess consciousness during seizures. To evaluate consciousness during seizures efficiently, both active patient-initiated behavioral techniques and passive patient responses to tests initiated by the examiner should be included. Therefore, we investigated two methods, one active (video game performance) and one passive (response to examination) to assess patients' consciousness during seizures.

Methods: For patient-initiated testing, three video games were studied: rFactor: a customized racing video game, SNIP: an open-source Tetris clone, and Frets on Fire: an open-source Guitar Hero clone. These computer-based games were played on a modified bed-side table with appropriate game controllers. Passive evaluation was assessed using the Responsiveness in Epilepsy Scale (RES) which included memory, motor, sensory and language function measurements. While monitored by 24 hour continuous video/EEG, patients with confirmed epilepsy were encouraged to play the video games as often as possible. A trained researcher at the patient's bedside detected seizure onset and repeatedly administered the RES procedures until all functions returned to the baseline level.

Results: Of the total 139 patients recruited, 44 were studied using only RES, 109 were observed utilizing only video games and 18 were tested by employing both. There were 64 male, 75 female, 117 right-handed, and 22 left-handed . Mean age was 35.6 years. Furthermore, 8 Intracranial EEG, 120 Scalp EEG, and 11 ictal SPECT patients were studied. Altogether, 30 seizures were captured from 14 patients during video games: 2 secondarily generalized, 14 partial, 5 absence, 6 auras, and 3 subclinical seizures. During RES evaluation, 34 seizures were captured from 16 patients: 4 secondarily generalized, and 30 partial seizures. The average seizure duration was 121 seconds. During subclinical seizures and auras, patients continued to play the video games. Patients stopped playing during secondarily generalized seizures. Impairment varied more in partial and absence seizures. According to the RES evaluations, the patients' responsiveness over time showed more severe impairment in secondarily generalized seizures compared with partial seizures. However, some functions were spared even during generalized seizures.

Conclusions: Our results demonstrate the feasibility of using standardized prospective behavioral techniques for assessing consciousness during various types of seizures. These approaches may ultimately help elucidate the anatomical structures of the consciousness network and delineate fundamental mechanisms of impaired consciousness in epilepsy.

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IMPROVING SAFETY OUTCOMES IN THE EPILEPSY MONITORING UNIT

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Rationale: Epilepsy monitoring using long term electroencephalography (EEG) and video to help classify and localize seizures is a common practice used by epileptologists when treating patients with medically intractable epilepsy and nonepileptic events. This is performed usually in designated epilepsy monitoring units (EMU) with the assistance of physicians, technicians, and nursing staff to monitor patients. To localize seizure onset and to classify seizure type, the physician must capture events typical for the patient. In the general population, epileptics have an increase risk of injury from seizures and seizure related falls. Injury is usually due to head and soft tissue injury, drowning, fractures, burns, and motor vehicle accidents. Despite care taken to insure the safety of patients off of medications, injury does occur due to seizures in the EMU. In an extreme case, an epileptic patient died in an EMU in Colorado as a result of their seizure after suffocating in a pillow overnight when staff resources were limited. Also, despite monitoring being a common practice, no set protocols exist on how to wean patients appropriately from their medications, how to properly care for a patient during a seizure in the EMU, how to properly arrange the physical environment in the EMU to ensure patient safety, how many seizures should be recorded, and how long to monitor patients. Our objective was to determine the frequency of seizure related injury and complications in the EMU and to identify what factors contributed to these complications including nursing care, technical issues, issues with the physical environment, and issues related to the seizures themselves. The goal ultimately is to highlight potential injury causing factors that may be common to all EMUs to drive the creation of formal standard guidelines for EMU monitoring.

Methods: We reviewed medical records and long term video EEG of epileptic patients admitted to our EMU from December 1, 2008 - June 1, 2009. Data was collected on seizure type, onset, length, and frequency. Seizure related falls, injury, and adverse events were recorded. Data regarding the physical environment and nursing care during seizures was analyzed too.

Results: 20 patients with 170 seizures were collected. 6 (30%) patients had seizure related falls, 1 with injury (5%), requiring further testing. 5 (83.3%) falls were related to patients being ambulatory. No seizures resulted in prolonged stay. Other adverse events included 1 status epilepticus (0.6%), 2 postictal aggression (1.2%), 4 objects in mouth during seizure (2.4%), 14 ambulatory during seizure (8.2%) and 5 postictal wandering (2.9%). Nurses were aware of 69 seizures (40.6%). The lack of response in most cases was due to electrographic seizures without seizure detection software or push button activation (57, 56.4%).

Conclusions: Falls and adverse events that can lead to injury occur in the EMU, yet the degree of actual injury is minimal. To improve safety outcomes, standardized protocols with appropriate outlined nursing care and procedures for continuous monitoring of patients by staff need to be employed.

1.227

HEAD TRAUMA AND EPILEPSY IN CHILDREN

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Rationale: Head trauma in children is the one of causes in epilepsy. The incidence of seizure after head trauma varies with the severity of brain injury, neurologic, neuroradiologic findings, and age. But for

epilepsy after head trauma it is not well known. We would like to know the incidence and the influencing factors of epilepsy after head trauma in children.

Methods: We reviewed retrospectively the medical records of 358 children with head trauma under 15 year old, who were admitted to the Wonju Christian Hospital from January, 2000 to December, 2005. The patients were divided non-seizure (NS) and seizure (S) after head trauma groups. In the S group, persistent seizures patients over 1 month after head trauma were defined epilepsy (E) group. We compared the characteristics of these three groups by severity of brain injury and other clinical variables such as age, sex, type of seizure, Grasgow Coma Scale (GCS)score, neurologic and neuroradiologic findings.

Results: The mean age was NS; 6.38±3.95 years, S; 4.90±3.81 years, and E; 5.48±3.01. The sex ratio (male:female) was NS; 1.8:1, S; 2:1, E; 6:1. The incidences of seizure and epilepsy after head trauma were 7.0% and 2.0%. The influencing factors of seizures after head trauma were abnormal initial neurologic findings such as hemiplegia and coma, duration of unconsciousness, GSC score under 12, and abnormal neuroimaging findings. But there was no different incidence rate by the severity of brain injury. The characteristics of E group were that the type of initial seizure was generalized tonic-clonic (85.7%); 57.1% had skull fracture; 71.4% had cerebral hemorrhage; 51.7% did brain operation; all patients showed abnormal neuroimaging findings of cerebral contusion.

Conclusions: We concluded the incidence of epilepsy after head trauma was lower than expected. The influencing factors for seizures after head trauma were abnormal initial neurologic findings such as hemiplegia and coma, duration of unconsciousness, GCS score under 12, and abnormal neuroimaging findings. Even though a large population studies will be necessary in the future, it may be influenced by severe brain injury to develop the epilepsy after trauma.

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FOCAL REFLEX EPILEPSY INDUCED BY VISUAL SPATIAL IMAGINATION

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Rationale: To describe a focal reflex epilepsy due to diffuse brain anoxia with seizures induced by cognitive tasks.

Methods: We performed EEG-video-monitoring in a 25 year old sport student who was buried by an avalanche resulting in hypoxia for ca. 15 minutes. He suffered a polytrauma and developed Lance-Adams-syndrome and focal motor epileptic seizures. We performed several cognitive tasks (variations of SUDOKU puzzles, mathematical and visual spatial imagination with letters and numbers) in order to elicit epileptic seizures during EEG-video-monitoring. High resolution 3T-MRI, diffusion tensor imaging (DTI), ictal and interictal single photon emission computer tomography (SPECT), and somatosensory evoked potentials (SEP) of the median nerve were performed.

Results: Despite the fact that his seizure were well controlled with a combination of 3g levetiracetam /d, 1,5g valproic acid /d and 13,6g piracetam /d, SUDOKU puzzles consistently induced clonic seizures of the left arm which would generalize secondarily when he would continue to find the correct solution. Ictal EEG showed right centro-parietal seizure pattern, which ceased immediately after SUDOKU was discontinued. The SUDOKU task was solved by the patient using a visual spatial approach. The SUDOKU as well as other visual spatial tasks like sorting random numbers in an ascending order consistently elicited clonic seizures of the left arm. MRI including DTI showed no pathological findings. Subtraction of ictal and interictal SPECT revealed hyperperfusion of the posterior gyrus cinguli. Left sided stimulation of the median nerve revealed increased right hemispheric SEP amplitude indicating decreased cortical inhibition over this hemisphere (amplitude left median nerve SEP 6,7uV compared to right median nerve SEP 2,7uV).

Conclusions: Diffuse brain anoxia may cause focal reflex epilepsy induced by cognitive tasks. This may be related to focal damage of U-fibers resulting in reduced cortical inhibition in the affected hemisphere.

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IS THERE A RELATIONSHIP BETWEEN ALLERGIES/ MEDICATION INTOLERANCES AND NONEPILEPTIC EVENTS?: A RETROSPECTIVE ANALYSIS

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Rationale: Non-epileptic events (NEE), as also known as psychogenic, non-epileptic seizures, are a common finding in an epilepsy monitoring unit. In clinical practice, we have noticed that patients with NEE tend to report multiple allergies and medication intolerances, which may be a characteristic of patients with somatoform or conversion disorders. We decided to retrospectively study if an increased number of medication allergies was more common in patients with NEE than patients with epileptic events (EE).

Methods: We performed a retrospective review of electronic medical records (EMR) of adult patients undergoing inpatient video EEG (VEEG) monitoring. We reviewed all VEEG reports completed in 2009 (N=361). Of the 361 patients whose VEEG reports were reviewed, only those whose reports documented either NEE (N=78) or EE (N=104) were included in the analysis. The number of medication allergies and intolerances were noted from the EMR.

Results: The average number of allergies and medication intolerances for patients with NEE and EE was 1.859 and 0.904 respectively (SD = 3.2 and 1.5, respectively. Analysis with the Wilcoxon non-parametric test showed that patients with NEE report a significantly higher number of allergies and medication intolerances than patients with EE ($p = 0.012$).

Conclusions: The results support the hypothesis that patients with NEE tend to report significantly more allergies and medication intolerances and suggest that this is one factor that may help predict that a patient has NEE versus EE.

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PREVALENCE OF DRUG RESISTANT EPILEPSY IN CHILDREN - ONE YEAR PROSPECTIVE STUDY IN TWO POLISH EPILEPSY CENTRES

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Rationale: To evaluate the prevalence of drug-resistant epilepsies among children and adolescents with epilepsy.

Methods: All epilepsy patients who entered the Developmental Neurology Departments (In and Outpatients Clinics) in the period between 01.10.2008 - 01.10.2009. were included in the study and followed prospectively. 1053 children and adolescents with dagnosed and treatet epilepsy entered the study. The diagnostic criteria for drug resistant epilepsy were : failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.

Results: 49% of patients fulfilled the criteria for drug-resistant epilepsy. The most common types of seizures among drug-resistant patients were complex partial seizures or polymorphic generalized seizures (tonic, tonic-clonic and myoclonic).

Conclusions: This large population based study shows according to recently proposed definition (Kwan et al. 2010) the surprisingly high incidence of drug-reistant epilepsies among children and adolescents.

Kwan, P., Arzimanoglou, A., Berg, A.T. et al. Definition of drug resistant epilepsy. Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies

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PSEUDO-GELASTIC SEIZURES IN A PATIENT WITH HYPOTHALAMIC HAMARTOMA AND POLYMICROGYRIA

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Rationale: We present a case of a 50 year old male with an extensive malformation of cortical development, predominantly affecting the right side and a hypothalamic hamartoma, discovered incidentally at the age of 43, following neurimaging after a motor vehicle accident. In the same year, he was found to have global hormonal insufficiency. Prior to this point he had never reported seizures. He became actively involved in a support organization for patients with brain tumors and subsequently developed multiple seizure types including one form that involved uncontrolled spells of laughter.

Methods: The patient, a 50 year old male with normal IQ, was admitted for video-EEG monitoring as a prelude to possible epilepsy surgery. He was accompanied at admission by a large stuffed animal which he kept in his bed throughout monitoring. He was monitored for 4 days during which 5 of his typical seizure-like events were captured

Results: Interictal EEG was normal. The seizure-like events started with his reporting right-sided tingling, followed by stereotyped non-clonic, right-sided hand movements, humming noises, calling out 'Mama' interspersed with repetitive spoken "ha-ha-ha" sounds, while inconsistently obeying commands to raise his arms or repeat words. After some of the episodes there was post-ictal weeping while clutching his stuffed animal.

Surface EEG remained completely normal throughout these events. One event was triggered by hyperventilation and events ranged in duration from 2 to 8 minutes.

Conclusions: The phenomenon of gelastic seizures in the setting of hypothalamic hamartoma is a classic presentation in neurology. It is not clear however, how frequent the finding is within the population of patients with hypothalamic hamartomas and it does not ocurr in all cases. Given the impressive neuroradiological findings in this case, the immediate clinical bias was to assume that the seizures were true gelastic seizures and to proceed with surgical work-up on this basis. Careful attention to the history revealed that seizures, including gelastic seizures, started only after the patient was alerted to the presence of the hamartoma and became aware of its associations. A weakness of this study is the fact that there was no depth recording from the hamartoma itself, however the clinical presentation of the events included numerous clues to a non-epileptic basis, a conclusion supported by a significant reduction in frequency of the laughing episodes after counseling, despite reduction in doses of anti-epileptic medications.

Another feature of interest in this case is that the presence of a stuffed animal, accompanying an adult with normal IQ to the Epilepsy Monitoring Unit was a sensitive indicator of non-epileptic seizures.

IMAGE: images/882340_A.jpg

Hypothalamic hamartoma

IMAGE: images/882340_B.jpg

Note stuffed animal in left hand

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PERIODIC LATE-ONSET SPASMS IN FOCAL SYMPTOMATIC EPILEPSY

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Rationale: Late-onset spasms (LOS) are epileptic spasms (ES) starting after the first year of life, usually resistant to treatment, found in patients with brain disorders and cognitive disabilities. Gobbi et al. (1987) first described a form of LOS in which periodicity is the most characteristic element; since then there has been no description of periodic LOS. Since ES could not be classified as focal or generalized the 2010 ILAE proposal for classification of epileptic seizures classified them under 'unknown' category. We describe periodic LOS and unique features in two children with Rasmussen encephalitis (RE) and focal cortical dysplasia (FCD).

Methods: Clinical, electroencephalographical and neuroimaging findings were assessed prospectively.

Results: Case 1 - A 5-year-old girl started presenting progressive left hemiparesis at 2.5 years followed, more than two years later, by clusters of asymmetric ES. Treatment with OCBZ was ineffective. Prolonged video-EEG monitoring revealed diffuse background slowing, more marked on the right hemisphere, and frequent spikes over the right frontotemporal (RFT) region. Stereotyped clusters of asymmetric periodic ES were recorded, associated with rictus-type facial grimaces, without consciousness impairment. EEG showed bursts of high voltage, generalized, symmetric, repetitive polyphasic slow spike-wave complexes, ranging from 0.5 to 2 seconds in duration, usually recurring every 5-13 seconds, with a typical diamond-shape on EMG recording.

Brain CT and MRI documented progressive atrophy of the right cerebral hemisphere, more marked over the perisylvian area. With presumable diagnosis of RE a right hemispherotomy was performed. Pathology confirmed the diagnosis, and the patient has been seizure free for six months. Case 2 - A 5-year-old boy started refractory daily seizures at 1.9 years and gelastic seizures at age of 4. Interictal EEG showed diffuse background slowing, more marked on the right hemisphere, and frequent spikes over the RFT region. Clusters of bilateral and symmetric ES were recorded, combined with laugh and rictus-type facial grimaces and preserved consciousness, accompanied by periodic RFT high-voltage slow waves with a superimposed fast rhythm, recurring every 2-3.5 seconds and a typical diamond-shape on EMG. A RFT FCD was suggested by MRI; he is currently waiting for surgery. Both children presented cognitive disabilities.

Conclusions: Whereas in West syndrome the majority of focal lesions involve posterior brain regions, LOS are associated with anterior lesions. As in Lennox-Gastaut syndrome, EEG abnormalities predominated in anterior areas in our cases of LOS. This sequence is likely to be determined by progressive maturation of the brain and it has been considered a new age-related epileptic encephalopathy. It has been suggested that periodicity of this intriguing pattern is the result of a diffuse or local alteration in neuronal excitability changing responsiveness to input from distant areas. The recognition of LOS in focal lesions is of paramount importance since it has implications in therapeutic and prognosis.

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SELF-INDUCED SEIZURES BY PERI-ORBITAL SOMATOSENSORY STIMULATION: A REPORT OF TWO CASES

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Rationale: Self-induced seizures by somatosensory stimulation are rare. We report two epileptic patients with self-induced seizures by peri-orbital somatosensory stimulation.

Methods: We investigated ictal video-EEG, interictal EEG, neuroimaging and clinical charts in two epileptic patients with self-induced seizures by peri-orbital somatosensory stimulation in National Epilepsy Center, Shizuoka Institute of Epilepsy and Neulorogical Disorders.

Results: Case 1: A 25-month-old girl was admitted to our hospital with a diagnosis of West syndrome. She had a history of acute subdural hemorrhage at 4 months of age and underwent two surgical excisions of the hematoma. MRI showed diffuse brain atrophy and her psychomotor development was severely delayed. From 7 months of age, she began to have serial seizures with flexions of both arms and head nodding. From 18 months of age, she started to rub her right eyelid with her right finger, and this behavior was followed by her habitual seizures. Ictal EEG showed right occipital sharp waves followed by diffuse low-voltage fast wave bursts after the eyelid rubbing behavior. These seizures stopped after she was prevented from rubbing her right eyelid. However, spontaneous habitual seizures relapsed. Case 2: A 5-year-11-months old boy was admitted to our hospital with a diagnosis of West syndrome. He had a history of acute subdural hemorrhage at 1 month of age and was treated conservatively. MRI showed diffuse brain atrophy and his psychomotor development was severely retarded. He developed West syndrome at 10 months. Seizures were temporarily controlled by ACTH therapy, but relapsed afterwards. From 2 years of age on, touching of his right eyebrow with the back of his left hand became evident. From 3 years of age, the above behavior was followed by serial seizures consisting of right arm flexion, left arm extension, and head nodding and deviated to the right. Ictal EEG showed bilateral occipital sharp waves followed by diffuse low voltage fast wave bursts after he touched his right eyebrow.

Conclusions: Attention should be paid to the presence of self-induced seizures in patients with severe pathology.

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WOLF - HIRSCHHORN SYNDROME PRESENTING WITH INTRACTABLE EPILEPSY AND DISTINCT UNILATERAL CUTANEOUS FINDING: A CASE REPORT

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Rationale: Wolf - Hirschhorn syndrome is one of contiguous gene syndromes due to deletion in the short arm of chromosome 4. The phenotype of these patients may vary depending on the extent of the deletion. Majority of patients clinically presents with seizures and other congenital abnormalities of the cardiac, renal, and skeletal systems. Rare reported cutaneous manifestations in this syndrome include skin tags, dry skin and hemangiomas.

Methods: A case report of Wolf - Hirschhorn syndrome in a child with intractable epilepsy presenting with a distinct unilateral cutaneous lesion and a possible cortical malformation ipsilateral to the cutaneous finding

Results: A 17 month old African American female was seen at 12 months of age during her first episode of febrile status epilepticus. Later she continued to present with unprovoked generalized tonic-clonic seizures and spasms. She was born at full term with significant low birth weight (intrauterine growth retardation). At 10 days of life she had a mild urinary tract infection and renal ultrasound showed bilateral renal cyst which persisted in her follow up scans. She had global developmental delay and her physical examination is significant for frontal bossing, high frontal hair line and a well defined café au lait spot occupying medial half of her left gluteal region to midline and extends to the upper one third of the left leg. No other café au lait spots or other cutaneous lesions were seen. Her neurological examination was significant for generalized hypotonia. EEG revealed multifocal epileptiform discharges predominantly in the posterior head regions. Her seizures were fairly controlled with a combination of topiramate, vigabatrin and clonazepam. MRI brain at 15 months of age showed increased perivascular spaces and lack of clear gray white differentiation over the left parieto-occipital region suspicious for a cortical malformation. Screening metabolic testing was unremarkable. Chromosomal microarray showed deletion (< 3.5 Mb) in the short arm of chromosome 4 (4p16.2p16.3) consistent with Wolf - Hirschhorn syndrome

Conclusions: This is the first case in the literature which illustrates another cutaneous finding that can be seen in patients with Wolf - Hirschhorn syndrome. The presence of a distinct unilateral cutaneous lesion in patients with Wolf-Hirschhorn syndrome and epilepsy should also direct the need to screen for possible epileptic cortical malformation ipsilateral to the side of the skin findings.

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BICYCLING DURING COMPLEX PARTIAL SEIZURES

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Rationale: Loss of consciousness during seizures is a factor which limits activity of patients with epilepsy. Driving restrictions is reported to have the most impact on quality of life and gained most attention. Testing individuals in the ictal state to determine ability to perform these activities has logisitcal difficulties. Bicycling is another activity of concern that the impact of seizures is unclear. We observed two patients who continued to use a stationary bicycle during part of VEEG recorded seizures.

Methods: Two patients with intractable seizures admitted for VEEG evaluation. Several seizures were recorded in both patients and each had one while using stationary bicycle.

Results: Patient 1 was a 43 year old male with a long history of intractable complex partial seizures. While using a stationary exercise bicycle, the patient continue to cycle for 30 seconds despite instructions to stop with simultaneous left temporal seizure activity. The second Patient 2 was a 25 year old male with frontal lobe epilepsy and generalized tonic-clonic seizures. This patient continued to pedal on the bicycle during 30 seconds of ictal generalized epileptiform pattern prior to tonic-clonic seizure.

Conclusions: Pedalling of stationary bicycle occurred during VEEG confirmed seizure activity thought to arise from temporal lobe in one and frontal lobe in the other patient. Loss of awareness was confirmed in one patient with lateralized seizure activity, and in the other generalized discharge was present. Although using a stationary bicycle may not require the same level of consciousness as cycling, these movements did persist during EEG seizure activity. This suggests that brief seizures during cycling may not result in adverse events related to loss of awareness and is worthy of further study.

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ELECTROENCEPHALOGRAPHIC CHARACTERISTICS OF SANDHOFF DISEASE (GM2 GANGLIOSIDOSIS)

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Rationale: Sandhoff disease (GM2 gangliosidosis) is a very rare neurodegenerative disease caused by deficiency of the enzymes Hexosaminidase A and B. We report the evolution of electroencephalographic (EEG) changes during the life of a patient with confirmed Sandhoff disease.

Methods: The patient presented at 12 months of age because of global developmental delay. His initial exam documented macrocephaly, hepatomegaly, axial hypotonia and appendicular hypertonia, hyperreflexia and ankle clonus. Ophthalmological examination confirmed the presence of cherry red spots. Lysosomal enzymes showed extremely low plasma levels of hexosaminidase A (14.6%) and hexosaminidase B (2%), confirming the diagnosis of Sandhoff disease.

Results: An initial routine EEG at 13 months was normal. At 16 months, he developed paroxysmal episodes of neck hyperextension. Video EEG documented that these episodes were not seizures. However, the EEG background had become abnormal, with poor organization of the frequency-amplitude gradient, frontal and temporal intermittent rhythmic delta activity, and frequent multifocal spikes. By age 21 months he was very irritable and spastic, and could not swallow. He had intermittent episodes of eye twitching followed by asymmetric bilateral facial twitching lasting up to 3 hours. Routine EEG confirmed the presence of subclinical seizures arising independently from the right temporal and left frontal regions, but clinical seizures were not recorded. The EEG background was slow, disorganized, and asymmetric, with suppression over the left hemisphere. There were generalized and independent right hemispheric subclinical electrodecrements, as well as multifocal sharp waves. He was treated with topiramate, but at a dose of 5mg/kg/day he developed new seizures with rhythmic leg twitching. Treatment was changed to phenobarbital 5mg/kg/day and the clinically-apparent seizures stopped. A swallow study documented aspiration. One month later, at age 22 months, he developed intermittent episodes of prolonged apnea. He was hospitalized and required intubation. EEG monitoring showed a diffusely suppressed and unreactive background. No seizures or sharp waves were recorded. The patient died a few hours later after the family elected to withdraw support. No autopsy was performed.

Conclusions: This report is the first to document the natural history of EEG features in a patient with Sandhoff disease. The serial EEGs in our patient documented progressive deterioration of the EEG background, evolving from a normal study at 13 months of age to focal and then generalized slowing and background disorganization, along with multifocal epileptiform discharges, electrodecrements, and focal seizures by age 21-months and then becoming unreactive and diffusely slow prior to his death at age 22-months. The EEG features mirrored the patient's clinical decline, with progressive neuromotor impairment and symptomatic epilepsy syndrome.

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ICTAL TREMOR IN A PATIENT WITH TEMPORAL LOBE EPILEPSY

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Rationale: Despite ictal tremor being reported for the first time over forty years ago, it remains a very rarely documented phenomenon. We can find some papers on familial cortical myoclonic tremor with epilepsy, but we were able to find just one paper on ictal tremors from 1966 (Harrington, Karnes, Klass, 1966). The authors reported involuntary movements in three patients which were clearly non-clonic in character. We would like to present the case of one of our patients with suspected ictal tremor. Three possible alternatives to tremor will be discussed: automatism, RINCH and myoclonus.

Methods: The case study

Woman, 19 years old; epilepsy since 13 years. No epilepsy reported in her family. Febrile seizures did not appear. Pharmacoresistant, average number of seizures 20 / 30 per month.

The MRI examination: right-sided mesiotemporal sclerosis (MTS), PET FDG: considerable hypometabolism on the temporal-right region.

Right-hander

Wada test proved supposed speech dominance of left hemisphere.

Electrophysiology: Inter-ictal as well as ictal semiinvasive video EEG finding is lateralized on right anteromedial area only.

Aura (palpitation, deja vu, deja vecu, gastric aura), complex partial seizure with perioral automatisms, extremity automatisms, ictal tremor of right upper extremity, dystonia of left upper extremity, ictal and post-ictal drinking water.

She had the AMTR epilepsy surgery 3 months ago and is seizure-free now.

Results: Clinical and neurophysiological findings

Ictal semi-invasive EEG proved that a seizure onset zone is located in the right temporal lobe.

Clinical semiology proved right-side localization of seizures onset zone; the right side is speech non-dominant.

There is no clinical finding of the ictal activity spreading to the left side.

Back averaging was negative.

EMG polygraphy results support the tremor diagnosis.

Discussion

In a temporal lobe epilepsy, a finding ipsilateral to seizure onset zone usually counts for automatism; however, our finding is of a rhythmic character, contrary to automatism.

The RINCH is rhytmic, contralateral, non-clonic, non-tremor hand-motion. However, our case is ipsilateral to the seizure onset zone and the recorded tremor is of a higher frequency than we can usually find in RINCH-movement cases.

Cortical myoclonus is indicated by rhythmic muscle activity. However, we did not find cortical potential preceding the followed phenomena in the course of back-averaging examination.

Conclusions: The findings point to a rhytmic, non-clonic character of movements and a relatively high frequency of the movement, which support the tremor conclusions. However, the ipsilateral seizure onset zone should be further explained. We suppose that our finding is a case of ictal activity which has spread to deep subcortical cerebral structures. On the other hand, we cannot rule out a possible spread of ictal activity to the left side.

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ANTICONVULSANT ACTIVITY OF PREGABALIN (LYRICA®) REQUIRES BINDING TO THE á$_2$ä$_1$ SUBUNIT OF VOLTAGE SENSITIVE CALCIUM CHANNELS

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Rationale: Pregabalin (Lyrica®) is approved in the U.S. as an adjunctive treatment for partial epilepsy. Pregabalin binds with high affinity to the á$_2$ä$_1$ and á$_2$ä$_2$ proteins of the voltage sensitive calcium channel. Mutagenesis studies have shown that a point mutant in á$_2$ä$_1$ (R217A) or in á$_2$ä$_2$ (R279A) removes binding of pregabalin to the á$_2$ä$_1$ or á$_2$ä$_2$ proteins.

Methods: These mutations have been introduced into mice to generate animals in which the wild type protein has been replaced by the mutant protein. C57BL/6N mice which are congenic for either the R217A mutation in á$_2$ä$_1$ or the R279A mutation in á$_2$ä$_2$ were tested in the mouse maximal electroshock model to determine whether the anticonvulsant activity of pregabalin changed by the mutations.

Results: Results show that the anticonvulsant activity of pregabalin in this model is eliminated in the á$_2$ä$_1$ mutants, but is identical to wild type in the á$_2$ä$_2$ mutants. Phenytoin is active in animals carrying either mutation.

Conclusions: These data show that the anticonvulsant activity of pregabalin arises from its interaction with á$_2$ä$_1$ subunits, not á$_2$ä$_2$ subunits.

Funded by Pfizer Inc.

IMAGE: images/901818_A.jpg

1.239

CARBAMAZEPINE INHIBITION OF SHARP WAVE-RIPPLE COMPLEXES IS ASSOCIATED WITH SYNAPSE-SPECIFIC EFFECTS ON NEUROTRANSMISSION AND SHORT-TERM PLASTICITY

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Rationale: Hippocampal sharp wave-ripple complexes (SPW-R) are proposed to participate in memory consolidation during periods of quiet and slow wave sleep. Previous reports have identified the CA3 region as the generation site of SPW-Rs with mossy fiber activity modulating their rate of incidence. Higher therapeutic concentrations of the antiepileptic drug carbamazepine are associated with cognitive side effects. Here, we determined carbamazepine effects on SPW-Rs, synaptic transmission and short-term plasticity (STP) at multiple hippocampal synapses.

Methods: Horizontal mouse hippocampal slices were placed on a high density multi-electrode array. Electrodes located in the Schaffer collaterals (SC) or mossy fibers (MF) were used to deliver paired pulse stimulations and evoke field potentials in the CA1 and CA3 regions. Spontaneous SPW-Rs were recorded in all regions before, during and after carbamazepine application.

Results: Results: The rank order of carbamazepine efficacy in inhibiting field potentials was SC-CA1>SC-CA3>MF-CA3. The potency order was SC-CA3>MF-CA3>SC-CA1. Carbamazepine was more efficacious inhibiting the second pulse field potential resulting in a ~25-30% decrease of the paired pulse ratio at all three synapses. All parameters of SPW-Rs were nearly abolished by 300 ìM carbamazepine with a potency similar to SC-CA3 inhibition. Regional representation of ripples was restricted to the CA3 region with increasing carbamazepine concentrations.

Conclusions: Carbamazepine inhibits SPW-Rs, field potentials, and STP at therapeutic concentrations associated with cognitive side effects. Synapse-specific sensitivity suggests that carbamazepine primarily inhibits the generation of SPW-Rs at CA3 recurrent collaterals. Carbamazepine inhibition at the MF-CA3 and SC-CA3 synapses most likely contributes by reducing the rate of incidence of SPW-Rs and preventing their propagation to the CA1 region.

1.240

ETHOSUXIMIDE TREATMENT INHIBITS EPILEPTOGENESIS AND ALLEVIATES BEHAVIOURAL CO MORBIDITIES IN THE GAERS MODEL OF ABSENCE EPILEPSY

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Rationale: No clinical therapies currently exist which combat epileptogenesis, the biological process(es) which transforms a healthy brain into an epileptic brain. Ethosuximide (ETX), a drug commonly used to reduce the occurrence of absence seizures in humans, has recently been shown to inhibit epileptogenesis in the WAG/Rij rodent model of idiopathic generalised epilepsy. Here, we investigated whether chronic ETX treatment was anti-epileptogenic in another polygenic rat model of absence epilepsy: the GAERS model. We also assessed whether drug treatment alleviated the behavioral abnormalities present in this strain.

Methods: At 3 weeks of age, GAERS (n=5) and non epileptic control (NEC, n=7) rats were weaned on to ETX in drinking water, and by 6 weeks of age (prior to the normal onset of seizures in GAERS), received an average of 300 mg/kg/day. This treatment was continued until week 22, when all rats were switched to tap water. Control-treated GAERS (n=6) and NEC rats (n=4) received tap water throughout the study. All rats underwent serial 24 hour EEG recordings for seizure expression and behavioral testing for anxiety levels.

Results: Prior to week 22 (when ETX treatment was ceased), ETX-treated GAERS spent significantly less time in seizure than control-treated GAERS (1.6 ± 0.5% vs 7.1 ± 1.1%; p=0.002). At week 34, at a time when ETX treatment had been ceased for 12 weeks, GAERS previously receiving treatment still exhibited significantly less seizure activity than controls (4.2 ± 0.4% vs 7.0 ± 0.7%; p=0.01). Anxiety levels, as assessed by total distance moved in the open field, were increased in GAERS compared with NEC rats, but this was reversed in ETX-treated GAERS, with a significant increase in distance travelled in treated GAERS compared with control-treated GAERS (3200 ± 701cm vs 2218 ± 275cm; p=0.04).

Conclusions: These data demonstrate that ETX induces an anti-epileptogenic effect in GAERS, reducing seizure expression long after treatment has ceased. Behavioural deficits were also reduced following cessation of treatment, intimating a common causation between seizures and anxiety in this model. The ability of this drug to limit disease progression in a second rat model validates the hypothesis that anti-epileptogenic therapy is achievable, and prevention of epilepsy in humans with early treatment may be possible.

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MODULATION OF SODIUM CONDUCTANCE BY PHENYTOIN IN RAT HIPPOCAMPAL CA1 CELLS IS MEDIATED THROUGH SLOW INACTIVATION PROCESSES

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Rationale: Phenytoin (PHT) is a commonly used anti-epilepetic medication, and, together with several other common AED's, most likely exerts its main pharmacological action by modulating voltage gated sodium (Nav)channels to reduce the amplitude of the depolarising sodium currents. There remains some uncertainty as to whether the action of PHT on Nav channels is caused by the fast inactivation process or via other inactivation mechanisms. To clarify this, PHT effects on both fast and slow inactivation processes have been studied.

Methods: Single pyramidal cells (n=36) from random sex 3-6 week old Wistar rats were isolated from the CA1 region using an enzymatic dissociation method. Cells were voltage-clamped using the whole-cell patch configuration, and PHT (50 uM)applied by a rapid perfusion system. Equilibrium states were measured with steady-state inactivation protocols using variable interval conditioning pulses, and transitions between closed/closed-inactivated states and open/inactivated states, as well as persistent current ("INap") amplitude were examined. Additionally, in some experiments, fast inactivation was removed with intracellular protease treatment. Effects of PHT in all theses conditions were observed.

Results: PHT shifted steady-state activation curves to the left (hyperpolarised), more so with longer pulses (500ms). Open-inactivated transitions were unaffected by PHT, and INap did not appear selectively reduced by PHT. Transitions between closed and closed inactivated states at potentials negative to threshold ~-60 mV) were strongly affected by PHT, but predominantly influenced components with longer time constants, rather than faster interconversions most likely related to the fast inactivation process. Entry into slow inactivated states became faster with PHT whereas exit was slower. PHT exerted proportionally the same reduction in amplitude of INa after enzymatic removal of fast inactivation. Recovery from fast inactivation was also largely unaffected by PHT.

Conclusions: PHT appears to modulate sodium channels mainly through slow or intermediate duration inactivation processes. This is surprising,as the effects of PHT have been generally ascribed to the fast inactivation process. It is likely that several other commonly used AED's have a similar mode of action.

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CSF AND PLASMA PHARMACOKINETICS OF ESLICARBAZEPINE ACETATE IN HEALTHY VOLUNTEERS

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Rationale: Eslicarbazepine acetate (ESL) is a novel, antiepileptic drug (AED) in development. ESL and oxcarbazepine (OXC) active metabolites (S-licarbazepine [eslicarbazepine] and R-licarbazepine) are formed in the periphery and cross the blood-brain barrier (BBB) to reach the voltage-gated sodium channel. It is unknown whether the metabolites differ in ability to cross the BBB and how the cerebrospinal fluid (CSF) concentrations correlate with their plasma concentrations.

Methods: Healthy volunteers were randomized to one of 2 treatment groups (ESL group or OXC group). Subjects were titrated over 3 days to target doses of 1200 mg QD of ESL or 600 mg BID of OXC, and treated from day 4 to day 9. Blood samples and metabolites level determinations were collected on Day 1 pre-dose and Day 9 pre-dose and 30 min, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose (16 and 24 h post-dose only in the ESL group). CSF samples for the ESL and OXC groups and metabolites level determinations were collected on Day 9 pre-dose and 30 min, 1, 2, 4, 6, 8, 12, 16 and 24 h post-dose (16 and 24 h post-dose only in the ESL group). Concentrations of eslicarbazepine, R-licarbazepine and OXC in plasma and CSF were measured and pharmacokinetic parameters determined. Tolerability of ESL and OXC was assessed. This study was approved by the applicable ethics committee.

Results: Fourteen subjects were randomized (7 ESL; 7 OXC) and treated. In the ESL group, the relative plasma exposure to eslicarbazepine, R-licarbazepine and OXC was 93.84%, 5.20% and 0.96% in plasma and 91.96%, 7.13% and 0.91% in CSF, respectively. In the OXC group, results were 78.06%, 18.47% and 3.47% in plasma and 76.42%, 21.36% and 2.22% in CSF, respectively. The apparent half-life of eslicarbazepine in plasma was approximately 16 hrs. and in CSF was approximately 24 hrs. The incidence of common treatment emergent adverse events is shown in Table 1.

Conclusions: In this study, in comparison to OXC, administration of eslicarbazepine acetate resulted in more eslicarbazepine, less R-licarbazepine and less OXC in plasma and CSF. The CSF half-life of eslicarbazepine was longer than the plasma apparent half-life; this has implications for dosing interval and may support once-daily dosing

Incidence of most commonly reported treatment emergent adverse events

IMAGE: tables/904662_T1.jpg

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CARBAMAZEPINE RESISTANCE IN HUMAN TEMPORAL LOBE CORTICAL NEURONS

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Rationale: The underlying mechanisms behind drug resistance in temporal lobe epilepsy (TLE) remain unclear. We studied the cellular response to carbamazepine in resected temporal lobe cortical tissue from patients with TLE.

Methods: 350ì slices of tissue were obtained from human and non-epileptic rat temporal lobe cortex. Voltage gated currents and excitability were monitored using whole-cell patch clamping standard protocols. Firing pattern analysis was done at the injected current level that produced reliable repetitive firing before and after perfusion with carbamazepine 50ìM . Biocytin 0.2% was then injected through the electrode in order to assess cell morphology and location using confocal microscopy.

Results: Carbamazepine suppressed high frequency neuron firing after current injection in both rat and human. All cells tested from non-epileptic rat brain slices (n=20) were sensitive to carbamazepine perfusion. Carbamazepine also suppressed firing in 10 of 14 human neurons but in 4 it had no effect. Morphological reconstruction of the patch-clamped cells in the rat revealed 9 pyramidal neurons and 11 interneurons. In the human cortex, 6 were pyramidal neurons and 8 were interneurons. The 4 cells that did not respond to carbamazepine were all interneurons.

Conclusions: Drug resistance to carbamazepine in TLE may relate to a failure to suppress high frequency activity of inhibitory interneurons.

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METFORMIN RESCUES ABERRANT PLASTICITY IN TSC2 MUTANT MICE VIA AMPK-DEPENDENT INHIBITION OF MTOR: THERAPEUTIC IMPLICATIONS

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Rationale: The mammalian target of rapamycin (mTOR) signaling pathway is a key regulator of cellular growth and protein synthesis-dependent long-term potentiation and depression (LTP and LTD, respectively). Emerging evidence implicates mTOR signaling in the progression of epilepsy. Recently we've shown that the energy sensor AMP-activated protein kinase (AMPK) can inhibit mTOR signaling to attenuate LTP. This suggests that AMPK activators such as the anti-diabetes drug metformin have therapeutic potential for treating neurological conditions of aberrant plasticity, such as epilepsy. Tuberous Sclerosis patients suffer cognitive impairment and epilepsy that are thought to be driven by hyperactive mTOR signaling and aberrant LTP induction. Therefore, we sought to assess the therapeutic potential of metformin in treating Tuberous Sclerosis.

Methods: In a mouse model of Tuberous Sclerosis (TSC2 heterozygous mutants), hippocampal plasticity (LTP and LTD) was characterized using slice electrophysiology in presence and absence of drug. To assess the effects of metformin on learning and memory, metformin was fed to TSC2 mutants and WT controls prior to a spatial learning paradigm. Biochemical evidence for the AMPK-mTOR signaling pathway was conducted to elucidate the mechanism of action for metformin.

Results: Here we provide evidence that activation of the metabolic sensor AMPK in TSC2 mutant mice can restore appropriate plasticity and are presently evaluating the effects on learning deficits. This phenotypic rescue is achieved through a TSC1/2 independent inhibition of mTOR signaling by AMPK.

Conclusions: Using an animal model of Tuberous Sclerosis, our results suggest that the widely used anti-diabetes drug metformin may have therapeutic potential in restoring cognitive function in TSC patients.

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LACK OF ASSOCIATION BETWEEN MULTIDRUG RESISTANCE 1 (MDR1) GENE POLYMORPHISMS IN CHILDHOOD DRUG RESISTANT EPILEPSY

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Rationale: Multiple drug resistance is a common problem in the treatment of epilepsy. The mechanism underlying the resistance to antiepileptic drugs may depend on the antiepileptic drug transport to epileptic focus. We investigated the association between polymorphism related to MDR1 in drug resistant epilepsy versus drug responsive patients.

Methods: DNA samples were obtained from 60 patients aged 2 to 18 years (mean: 9.28+4.96) with drug responsive epilepsy, 59 patients with drug resistant epilepsy aged 2 to 16 years (mean:6.68+4.21) and

76 unrelated healthy subjects. Genotype of the C3435T polymorphism was determined by polymerase chain reaction followed by melting curve analysis. Results were expressed as genotype and allele frequencies per drug response, drug resistant and healty control group and compared by X2 -test.

Results: Genotype frequencies in drug resistant patients were as follows; 32.2 % CC, 44.1 % CT, 23.7 % TT, in drug responsive group; 20 % CC, 50 % CT, 30 % TT, in control group; 24.3 % CC, 50 % CT, 25.7 % TT. Comparison of drug resistant and drug responsive patients revealed no significant difference in genotype frequency (p:0.31). The findings in the epilepsy patients were not significantly different from the healty control subjects (p: 0.92).

Conclusions: There are conflicting data as to whether the CC or TT genotype of the 3435C>T polymorphism is associated with drug resistance. Our study did not support any significant association between the MDR1 polymorphism and drug resistant childhood epilepsy.

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CHRONIC ANTAGONISM OF NMDA RECEPTORS (NMDAR) WITH THE NR2B-SELECTIVE ANTAGONIST, RO25-6981 SUPPRESSED WHILE THE HIGH-AFFINITY COMPETITIVE ANTAGONIST, D-APV EXACERBATED SEIZURE SUSCEPTIBILITY IN A CONCENTRATION-DEPENDENT MANNER IN ORGANOTYPIC HIPPOCAMPAL CULTURES

Angelique Regnier-Golanov, Y. Dong and S. B. Bausch (Pharmacology, Uniformed Services University School of Medicine, Bethesda, MD)

Rationale: We documented previously that chronic treatment with Ro25-6981 (Ro; 1μM) attenuated susceptibility to seizures induced by bicuculline (BMI) in hippocampal cultures as shown by decreased seizure duration and number (Wang & Bausch, 2004). This effect persisted for at least 24 hr after Ro removal and was accompanied by reduced neuronal death and mossy fiber sprouting. In contrast, chronic treatment with D-APV (50μM) exacerbated BMI-induced seizure susceptibility, neuronal death, and mossy fibers sprouting. In this study, we examined the concentration dependence of Ro and APV effects on susceptibility to seizures induced by BMI or removal of Mg2+ from the recording buffer.

Methods: Hippocampal slices obtained from P11 S/D rats were cultured for 17 to 21 days in media containing increasing concentrations of Ro or APV. Drugs were omitted from media for controls. After chronic treatment, slices cultures were superfused with artificial cerebrospinal fluid (aCSF, 32-34C) for 30min to remove drugs. Field potentials were recorded from the suprapyramidal blade of the dentate granule cell layer for 45min. Seizures were induced either by perfusion with aCSF without Mg2+ (0Mg2+) to increase glutamatergic excitation or by aCSF containing BMI (10μM) to suppress GABAergic inhibition.

Results: As expected, BMI-induced seizures were suppressed following chronic treatment with Ro in a concentration dependent manner. At 1μM, Ro significantly ($p<0.05$) decreased total seizure duration and number by 72% and 58%, respectively and increased the latency to first seizure by 95%. Interestingly, 0Mg2+-induced seizures displayed a biphasic concentration-response curve following chronic treatment with Ro. At 1nM, Ro significantly increased total seizure duration and number by 55% and 60%, respectively and reduced the latency to first seizure by 12%. At 1μM, Ro significantly decreased total seizure duration and number by 65% and 57%, respectively and increased the latency to first seizure by 22%. In contrast, both BMI- and 0Mg2+-induced seizures were exacerbated in a concentration-dependent manner following chronic treatment with APV. At 50 μM, APV significantly: 1) increased total seizure duration by 266%, 0Mg2+, 60%, BMI; 2) increased seizure number by 106%, 0Mg2+, 74%, BMI; and 3) reduced the latency to first seizure by 53%, 0Mg2+, 39%, BMI.

Conclusions: These data show that chronic treatment with Ro and APV exerted opposite, concentration-dependent effects on seizure expression. The exception was the potential epileptogenic effect of 1nM Ro for 0Mg2+ -induced seizures, which may be attributed to a differential selectivity of Ro for bi- versus triheteromeric NMDAR in GABAergic interneurons.

1.247

INVESTIGATION OF LACOSAMIDE BINDING TO COLLAPSIN RESPONSE MEDIATOR PROTEIN-2 (CRMP-2)

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Rationale: Lacosamide (LCM, SPM 927, Vimpat) is an antiepileptic drug recently approved in the USA and Europe as add-on treatment for partial onset seizures. LCM presents a novel mode of action by selectively enhancing sodium channel slow inactivation without affecting fast inactivation which differentiates it from classical antiepileptic drugs (Errington *et al.*, 2008). Initial investigations proposed that LCM might have an additional mode of action by interacting with the collapsin response mediator protein CRMP-2 (Beyreuther *et al.*, 2007). In the present study we describe the investigation of LCM binding to the cloned human CRMP-2 protein using different biochemical and biophysical experimental approaches.

Methods: The human CRMP-2 protein was transiently expressed with or without tags (6xHis, GST) in a variety of mammalian cells (HEK, COS) and *Xenopus laevis* oocytes (mRNA injection). Membrane fractions were prepared and CRMP-2 protein levels were verified by Western Blot. Experiments carried out on isolated CRMP-2 protein used tagged hCRMP-2 (His-C_t; GST-N_t) that was expressed and affinity purified from *E. coli* and coupled to scintillation proximity assay (SPA) beads. Specific binding of [^{3}H]LCM (specific activity: 31 Ci/mmol, free concentration range: 100-1450 nM) was assessed on isolated and membrane bound CRMP-2 protein using classical filtration binding assays or scintillation proximity assays. Non-specific binding was determined in the presence of 1 mM LCM. The binding of unlabelled LCM to the histidine-tagged hCRMP-2 was investigated by surface plasmon resonance (Biacore, GE Healthcare) using a CM5 sensor chip.

Results: The hCRMP-2 protein was efficiently expressed in membrane fractions from mammalian cells and *Xenopus* oocytes (~500ng/100μg membranes) and binding of [^{3}H]LCM was investigated under various experimental conditions (25°C or 37°C; different buffer compositions). We observed no specific binding of [^{3}H]LCM (free concentration 100-1450nM) to the hCRMP-2 protein expressed in membrane fractions or to the isolated tagged hCRMP-2 protein coupled to SPA beads under all experimental conditions tested. Biacore analysis showed that LCM over a concentration range of 0.39-100μM does not specifically bind to the hCRMP-2 protein.

Conclusions: Previous investigations, using [^{14}C]LCM, indicated that LCM may bind to the hCRMP-2 protein with a dissociation constant of ~5 µM (Beyreuther *et al.*, 2007). In this study we attempted to further characterize this putative binding site of LCM by using either [^{3}H]LCM (having 1000 fold higher specific activity than [^{14}C]LCM) or by measuring direct binding of unlabelled LCM to purified hCRMP-2 using surface plasmon resonance. Although these methods were well suited to measure binding affinities in the µmolar range, the results obtained were all negative. In conclusion, the present study, using a wide variety of experimental approaches, does not support the presence of a specific binding site for LCM on the hCRMP-2 protein.
References: Beyreuther *et al.* CNS Drug Reviews 2007;13(1):21 & Errington *et al.* Mol Pharmacol. 2008;73:157

1.248

DEVELOPMENT OF PHENYTOIN RESISTANCE IN POST-TRAUMATIC EPILEPTOGENESIS

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Rationale: Traumatic brain injury is a major cause of acquired epilepsy. Phenytoin prevents acute post-traumatic seizures but not post-traumatic epilepsy. We studied the effects of chronic application of phenytoin on epileptogenesis, seizures, and cell death to elucidate the origins of phenytoin resistance and develop new therapeutic strategies.

Methods: We used organotypic hippocampal slice cultures as a model of severe traumatic brain injury. Slices were incubated in medium containing phenytoin, the broad-spectrum glutamate antagonist kynurenic acid, the calcineurin antagonist FK-506, or vehicle for up to six weeks. Electrophysiological activity and cell death were monitored via electrode arrays and confocal imaging of propidium iodide uptake, respectively. Sub-cellular localization of NFATc4 was determined with immunohistochemistry as an assay for calcineurin activation.

Results: Continuous electrical recordings revealed progressive development of spontaneous epileptiform discharges, including interictal spikes, ictal-like tonic-clonic seizure activity and electrical status epilepticus over the first 3 weeks of culture. We found that seizures accelerated neuronal death, and that cell death was highly correlated with Ca2+ entry and activation of calcineurin. Cell death was dramatically reduced by blockade of glutamatergic transmission with kynurenic acid, by eliminating ictal-like discharges and status epilepticus with phenytoin, and by inhibiting calcineurin with FK-506. Removal of kynurenic acid or phenytoin from incubation medium was followed by a sharp increase in seizure activity. We also found that after four weeks, chronic incubation with phenytoin was no longer effective at controlling seizures or preventing cell death.

Conclusions: Our experimental data supports clinical findings indicating that chronic anticonvulsant therapy improves seizure control but does not prevent post-traumatic epileptogenesis, and does not prevent drug-resistant epilepsy. We extend the clinical data by showing that despite a lack of effect on epileptogenesis, seizure control reduces neuronal death. We will use this model to explore post traumatic epileptogenesis, mechanisms of medical intractability, and neurodegeneration in intractable epilepsy.

1.249

ATRIAL FIBRILLATION AND VENTRICULAR TACHYCARDIA IN PATIENTS WITH PARTIAL SEIZURES TREATED WITH LACOSAMIDE

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Rationale: Lacosamide (LCM) is a novel anti-epileptic drug that enhances slow inactivation of voltage-gated sodium channels. In clinical trials in diabetic peripheral neuropathy, LCM was associated with cardiac conduction defects (AV block) in 0.5% and atrial fibrillation in 0.5%. In clinical trials in epilepsy, conduction defects (AV block) occurred in 0.4%; atrial fibrillation has not been reported. We report two cases of serious cardiac arrhythmias possibly associated with LCM treatment for partial seizures.

Methods: Case Series: Two patients at the UCLA Seizure Disorders Center who sustained severe cardiac arrhythmias (acute atrial fibrillation and acute sustained ventricular tachycardia) during LCM treatment were identified. Hospital and clinic records, cardiology consultations, electrocardiograms (ECG) and electrophysiological studies were evaluated.

Results: Case I. A 37 year-old female with intractable partial seizures and no cardiac risk factors was initiated on LCM as adjunctive therapy. While on LCM 600 mg/day and Lamotrigine 300 mg/day, the patient experienced sudden onset of rapid heartbeat, palpitations, and lightheadedness. Upon hospitalization, an ECG detected atrial flutter/atrial fibrillation with a rapid rate of 136 bpm. Warfarin and a calcium channel blocker were initiated. Her dosage of LCM was reduced to 400 mg/day, but on reevaluation three weeks later, atrial fibrillation persisted. A decision was made to taper and discontinue LCM by 100 mg/week. An ECG one week after cessation of LCM showed complete resolution of atrial fibrillation/flutter. Atrial fibrillation has not recurred in the six months since discontinuation.

Case II. A 49 year-old male with severe intractable frontal lobe seizures was initiated on LCM 400 mg/day as adjunctive therapy in addition to preexisting Carbamazepine, Lamotrigine, Clonazepam, and Valproate. The patient had no prior history of cardiac arrhythmias, but had well controlled hypertension and hypercholesterolemia, treated with atorvastatin, valsartan, and triamterene. A cardiac stress test prior to the addition of LCM demonstrated no abnormalities. While undergoing a repeat cardiac stress test, he experienced sustained ventricular tachycardia, which required acute stabilization and hospitalization. LCM was tapered by 100 mg/day until discontinued. Repeat electrophysiological study 24 hours after discontinuation of LCM was normal. An ECG loop monitor was implanted. There has been no recurrence of the arrhythmia at four months following discontinuation of LCM.

Conclusions: Adjunctive treatment with LCM in two patients with intractable partial seizures was associated with severe cardiac arrhythmias. The onset of the arrhythmias while on LCM, followed by resolution after discontinuation of LCM, provides evidence of a possible link to LCM. Given evidence of arrhythmias in clinical trials in diabetes, and the possible association of LCM with arrhythmias in our patients, physicians should be alert to the potential for cardiac arrhythmias in patients with epilepsy treated with Lacosamide.

1.250

CARBAMAZEPINE DIRECTLY MODULATES MITOCHONDRIAL FUNCTION IN WILD-TYPE AND EPILEPTIC MICE

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Rationale: Mitochondrial dysfunction, including impairment of respiratory capacity and ATP production, excessive free radical generation and lowered mitochondrial permeability transition occurs in seizure-genic regions such as the hippocampus in animal models of epilepsy. We examined whether the antiepileptic and neuroprotective drug carbamazepine (CBZ) directly influences mitochondria function.

Methods: Mitochondria were isolated from the hippocampus of normal wild-type and chronically epileptic Kcna1-null mice. Respiratory capacity, calcium sequestration and reactive oxygen species production were assessed using standard oxygen polarography with a Clark-type electrode and spectrofluorescence assays.

Results: Hippocampal mitochondria was dysfunctional in Kcna1-null mice, specifically, state III respiration was impaired when compared to that of wild-type control mice. Application of CBZ attenuated state III respiration in wild-type hippocampus in a concentration dependent manner (IC50: 129.2μM). In contrast, CBZ failed to influence the respiratory capacity of hippocampal mitochondria isolated from epileptic mice at all concentrations examined (50-300 μM). Furthermore, CBZ differentially influenced the ability of wild-type and pathologic mitochondria to sequester calcium and generate free radicals.

Conclusions: These data indicate that CBZ directly influences mitochondria function and suggest novel anti-epileptic mechanisms in its ability to influence energy regulation and neuroprotective signaling cascades. In addition, the lack of effect of CBZ in epileptic mitochondria supports the notion that dysregulation of mitochondrial proteins will impede normal function and may contribute to the ineffectiveness of CBZ in certain medically refractory epilepsies.

1.251

CHLORIDE COTRANSPORTERS NKCC1 AND KCC2 EXPRESSION IN RAT AND HUMAN RETINA

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Rationale: Rationale: Vigabatrin (VGB) was recently approved by the FDA for the treatment of infantile spasms and refractory seizures. However, a major limiting factor to its use is the high incidence of retinal toxicity and bilateral visual field deficits in approximately 30% of treated patients. Human studies and rat models of VGB toxicity show that the retinal injury involves ganglion cell death (Duboc et al, Ann Neurol, 20 2004;55:695-705). The mechanism of this toxicity is poorly understood. Given that VGB increases retinal and brain GABA concentrations, we hypothesized that retinal injury might occur secondary to the presence of depolarizing GABA receptor responses and subsequent excitotoxic ganglion cell death. The presence of the NKCC1 chloride co-transporter is necessary for the paradoxical depolarizing GABA receptor mediated responses. As ganglion cells have GABA receptors, we hypothesized that NKCC1 may be expressed on ganglion cells in rat and human retina.

Methods: Methods: We examined whether NKCC1 is expressed in rat and human retina using immunocytochemistry with NKCC1 antibody (Aviva Systems Biol., 1:300; Developmental Studies Hybridoma Bank, 1:500) and KCC2 (Upstate/Millipore, 1:500). Adult Long Evans rats were perfused with 4% PFA and the eyes (n=4) processed for cryosectioning. Human retinas (n=10) were fixed in formalin and embedded in paraffin and antigen retrieval was performed with citrate buffer. 20 μm sections were stained for anti-NKCC1 and anti-KCC2 antibodies.

Results: Results: In rat, NKCC1 expression was seen in horizontal, amacrine and ganglion cell somas as well as in the OPL in the synaptic terminal region. KCC2 expression was present in amacrine cells, horizontal and bipolar cells and ganglion cells as well as in OPL in the terminal processes and intense labeling in the entire neuropil area of the IPL. Similar patterns were observed in the human retina: NKCC1 was present in horizontal, amacrine cells and ganglion cell somas.

KCC2 present in horizontal, amacrine and bipolar cells and ganglion cells as well as in the IPL.

Conclusions: Conclusion: Taken together, these data suggest that NKCC1 is present in both rat and human eyes in a cell population that has been previously shown to be vulnerable to vigabatrin toxicity. In addition, human eye immunocytochemistry suggesting that depolarizing GABA responses may play a role in retinal toxicity due to VGB. Future studies will test the efficacy of bumetanide, an NKCC1 inhibitor, in preventing VGB induced retinal toxicity in a rat VGB model.(Supported by grants #:1RC1NS068938-01 and P3O HD 18655)

1.252

LACOSAMIDE ATTENUATES CORTICAL EXCITABILITY IN THE RAT CORTICAL STIMULATION MODEL

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Rationale: Lacosamide is a novel antiepileptic drug which is currently used as an add-on treatment for partial seizures with or without secondary generalisation. Its anti-seizure effect is believed to result from a selective enhancement of the slow inactivation of voltage-gated sodium channels. Lacosamide is effective in the maximal electroshock model, the kindling model and the pentylenetetrazol model. The effect of lacosamide on cortical excitability has not been studied in vivo. Our aim in this study was to evaluate the effect of lacosamide on motor cortex excitability in the cortical stimulation model (CSM). In the CSM, a ramp-shaped pulse train with increasing intensity is delivered through epidural electrodes placed over the motor cortex. The threshold intensity for eliciting forelimb clonus is determined through behavioural observation, and is used as a measure for cortical excitability. Several known antiepileptic drugs including diazepam and carbamazepine increase threshold intensity in this model. Benefits of the CSM are that the activity of a drug can be accurately, rapidly and repeatedly determined in the same animal with a short interval between measurements. The CSM is useful for dose-finding and pharmacokinetic studies.

Methods: Male Wistar rats (145-220g) were surgically implanted with epidural stimulation electrodes positioned over the motor cortex (AP: -1 mm; ML: +/-3 mm). Following surgery, animals were allowed to recover for one week. Subsequently, all animals were stimulated twice

daily for 10 days (ramp pulse 0-1 mA, 50 Hz, pulse width 2 ms) to obtain a stable threshold intensity to forelimb clonus. A first group of 7 stabilized animals underwent intraperitoneal (i.p.) administration of 0, 2.5, 5, 10 and 20 mg/kg lacosamide in a random order on 5 consecutive days. Threshold intensity was determined 1 h before and 30 min, 2 h and 5 h after every injection. To determine whether tolerance to lacosamide occurs after repeated administration, a second group of 7 animals underwent i.p. administration of 20 mg/kg lacosamide once daily on 5 consecutive days.

Results: During the stabilization period (stimulation days 1-10), threshold intensity to forelimb clonus decreased from 605 +/- 37 µA to 350 +/- 34 µA (n=20). Lacosamide increased the threshold intensity to forelimb clonus in a dose-dependent manner: 2.5, 5, 10 and 20 mg/kg lacosamide increased threshold intensity by 30 +/- 20%, 55 +/- 24%, 47+/- 10% and 94 +/- 24% respectively. Threshold intensity reached a maximum 30 min after injection of lacosamide and returned to baseline 2 h after injection. Administration of 20 mg/kg lacosamide on 5 consecutive days did not result in attenuation of its effect on cortical excitability.

Conclusions: Lacosamide decreases cortical excitability in the CSM in a dose-dependent manner. The effect of lacosamide on cortical excitability was maximal 30 min after injection of the drug, and lasted for 2 h. This suggests that lacosamide's half-life may be shorter in rodents than in humans (13 h). Repeated administration of a high dose of lacosamide on consecutive days did not result in tolerance.

1.253

ASSESSMENT OF SEIZURE CLASSIFICATION IN MULTINATIONAL, MULTICENTER ANTIEPILEPTIC DRUG TRIALS

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Rationale: In order to attain optimal results from multicenter, multinational clinical trials, it is important to ensure homogeneity and accuracy in seizure classification. The Epilepsy Study Consortium reviewed seizure classifications for accuracy in subjects with treatment resistant partial onset seizures enrolled in a multinational investigational study sponsored by Supernus Pharmaceuticals, Inc.

Methods: Sites were required to submit seizure identification forms immediately following Visit 1. Each form contained a detailed description of the subject's seizures and the seizure classification. This information was submitted to the Consortium and reviewed for accuracy for the first two subjects enrolled at each site. Discrepancies were followed up by one of the consortium's reviewers until resolved. After two forms were reviewed with no corrections, the site was approved. If corrections were required, the Consortium continued to review every subject's seizure identification form until approval criteria was met.

Results: A total of 231 forms, containing 514 separate seizure descriptions and classifications were reviewed and reconciled. The following countries participated in this study: North America (USA, Canada, Mexico) and Eastern Europe (Bulgaria, Croatia, Poland, Romania, Russia).

One or more seizures were misclassified on 29/231(13%) of the forms. Overall, 36/514 (7%) of the seizures were misclassified. The % of seizures within category that were misclassified were as follows: SPS w/o motor: 4%, SPS w/motor: 11%, CPS: 8%, 2°GTCC: 1%.

Misclassifications by region: North America submitted 13/82 forms (16%) that contained at least 1 misclassified seizure and Eastern Europe submitted 16/149 (11%).

Misclassifications by country: Only countries with more than 10 forms were assessed. The country with the highest number of misclassifications submitted 5/24 incorrect forms (21%) and the lowest had 0 (0%).

See table below.

Other Misclassifications:

Ï% 2 seizure types were combined into 1 (should have been captured separately)

Ï% Seizure was non-epileptic and removed in the 2nd version

Ï% Investigator was unsure how to classify seizure

Ï% After asking for clarification, new seizure types were added

One subject experienced only simple partial seizures that were not observable and did not qualify for the study. The site classified the seizure correctly; however this subject may have been randomized if the review had not been performed.

For this particular trial, SPS without an observable component will not be analyzed in the efficacy analysis. The 4 seizures that were classified incorrectly as SPS w/o motor would not have been included in the analysis.

Conclusions: Seizure misclassification is frequent enough to warrant oversight at the time of enrollment. In a number of cases, identified errors in classification could have impacted trial results.

IMAGE: tables/904860_T1.jpg

1.254

EFFICACY OF RETIGABINE AS ADJUNCTIVE THERAPY IN TWO RANDOMIZED TRIALS IN ADULTS WITH DRUG-RESISTANT PARTIAL-ONSET SEIZURES: PER-PROTOCOL POPULATION ANALYSIS

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Rationale: Retigabine (referred to as ezogabine in North America) is a first-in-class antiepileptic drug (AED) that reduces neuronal excitability by enhancing the activity of KCNQ (Kv7) potassium channels. In the Retigabine Efficacy and Safety Trials for Partial Onset Epilepsy (RESTORE 1 and 2), retigabine 600, 900, and 1200 mg/day proved effective and was generally tolerated as adjunctive treatment for adult patients with partial-onset seizures. This report presents an analysis of the RESTORE 1 and 2 per-protocol populations.

Methods: RESTORE 1 and 2 (Studies 301 [NCT00232596] and 302 [NCT00235755]) were multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase III trials in adults with refractory epilepsy and e"4 partial-onset seizures per 28 days, receiving 1-3

AEDs, with or without vagus nerve stimulator. Patients were randomized to retigabine or placebo (administered tid) and underwent forced-titration to 600 or 900 mg/day (RESTORE 2) or 1200 mg/day (RESTORE 1) followed by a 12-week maintenance phase. One dose reduction to 1050 mg/day was allowed at the first maintenance phase visit in RESTORE 1. The changes in 28-day total partial-seizure frequency and responder rate (e”50% reduction in baseline seizure frequency) from baseline to maintenance were assessed and analyzed for the per-protocol population, which included protocol completers without major protocol violations.

Results: In RESTORE 1 and 2, 305 and 538 patients respectively, were randomized to retigabine or placebo and received e”1 dose of study drug (RESTORE 1: 1200 mg/day, n=153; placebo, n=152; RESTORE 2: 600 mg/day, n=181; 900 mg/day, n=178; placebo, n=179). The per-protocol populations for RESTORE 1 and 2 totaled 211 and 396, respectively (RESTORE 1: 1200 mg/day, n=89; placebo, n=122; RESTORE 2: 600 mg/day, n=130; 900 mg/day, n=117; placebo, n=149). In the RESTORE 1 per-protocol population, median reduction in seizure frequency from baseline to maintenance for retigabine 1200 mg/day vs placebo was 56.7% vs 20.0% ($p<0.001$), with responder rates to maintenance of 60.7% vs 21.3% ($p<0.001$). In the RESTORE 2 per-protocol population, median reduction in seizure frequency from baseline to maintenance for retigabine 600 and 900 mg/day vs placebo was 37.7% and 50.6%, vs 16.7% (pd”0.001 each), with responder rates to maintenance of 38.5% and 50.4%, vs 18.8% ($p<0.001$ each). Although safety and tolerability were not assessed separately in the per-protocol populations, retigabine was generally well tolerated in the overall safety population as presented previously.

Conclusions: In these studies, retigabine 600, 900, and 1200 mg/day were effective compared with placebo in adults with drug-resistant epilepsy and partial-onset seizures in the per-protocol populations, similar to the intent-to-treat populations previously reported.

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1.255

ADJUNCTIVE THERAPY WITH LACOSAMIDE FOR EXTREMELY REFRACTORY EPILEPSY IN CHILDREN

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Rationale: Lacosamide (LCM) is approved as adjunctive therapy in adults 17 years and older for partial onset seizures. LCM may benefit children who have failed to respond to previous antiepileptic drugs (AEDs). However, little is known about the use of LCM in children. We have reviewed our records and report our experience on dose, efficacy and adverse effects of LCM in children.

Methods: Following IRB approval, patients < 17 years old who had been treated with LCM between May 2009 and May 2010 were identified. Medical records were audited for demographics, EEG/MRI, seizure type/frequency, previous/current treatments for seizures, and information regarding treatment with LCM, dosing regimen, efficacy and adverse effects (AEs).

Results: Thirty patients (15 female, 15 male), median age 8 years (range: 17 months-16 years), were treated with LCM. 22/30 (73%) have a significant related structural abnormality identified on MRI and 21 (70%) have severe/profound cognitive impairment. Median failed past AED trials 10(range 5-18). LCM was added to 1-5 concomitant AEDs (90% e” 2 AEDs). The mean starting dose was 2.2 (range: 0.54-8.64) and maximum dose 8.4 (range: 2.74-18.8) mg/kg/day. 7/30 (23%) had a e” 50% reduction of seizures from baseline (mean dose 7.8 mg/kg/day) with 2 (6.6%) seizure free for 52 and 37 weeks. 18/30 (60%) continue LCM with duration of therapy at last contact of 4-52 weeks. 16/30 (53.3%) reported 26 total AEs regardless of association to LCM (mean dose 8 mg/kg/day) compared to 14/30 without AEs (9 mg/kg/day). Most frequently reported: ataxia (23.3%), sedation (23.3%), vomiting (10%) at mean doses of 10, 9 and 15 mg/kg/day respectively. 16/30 (53%) had LCM added to a regimen containing an AED with a primary mechanism of voltage-gated Na+ channel blocker. 10/16 (62.5%) reported AEs (7/10 LTG, 1/3 OXC, 1/2 CBZ, 1/1 RUF): mean dose 5.24 mg/kg/day (LTG group) and 13.73 mg/kg/day (others combined). 14/30 patients whose LCM was added to non-primary Na+ channel blocker AEDs, 6 reported AEs (mean dose 8.2 mg/kg/day). No significant abnormal lab values or serious AEs were reported. EKG was not routinely performed. 12/30 (40%) discontinued LCM. 9/30 (30%) due to lack of acceptable benefit and 3 (10%) due to AEs (mean maximum dose 8.9 and 3.3 mg/kg/day respectively). 7/30 had 9 random LCM levels drawn. Levels of 1.8-8.3 mg/L were documented on 3.67 - 14.2 mg/kg/day and not clearly associated with efficacy or tolerability.

Conclusions: Lacosamide demonstrated efficacy and tolerability as adjunctive therapy in children with refractory epilepsy. Almost one in every 4 patients had a e” 50% improvement in seizure control with 2 patients (6.6%) seizure free. There were no serious adverse effects; no clinically significant abnormal lab values. In this very small group, more AEs were observed at relatively lower doses when LCM was added to LTG. When LCM is added as adjunctive therapy to multi-AED therapy, in general, an initial starting dose of 2 mg/kg/day to a maintenance dose of up to 8 mg/kg/day is tolerated.

1.256

THE IMPACT OF STANDARDIZATION ON THE MAGNITUDE OF TREATMENT EFFECT WHEN ANALYZING LOG-TRANSFORMED SEIZURE OUTCOME

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Rationale: The choice of primary endpoint to support the regulatory approval of an antiepileptic drug as add-on therapy for focal epilepsy is not agreed upon. Recently, more sophisticated statistical methodologies have been applied to analyze seizure outcomes, including the application of parametric statistical methods after transformation of seizure frequencies. While these methodologies have advantages, there are also critical considerations when applying these methods.

The purpose of this analysis was to evaluate the impact of alternative standardizations of partial onset seizure (POS) frequency when analyzing log-transformed outcome.

Methods: Seizure data from two randomized, double-blind, placebo-controlled trials (N01252/N01253) evaluating the efficacy and tolerability of adjunctive brivaracetam (BRV) in patients with uncontrolled focal epilepsy were used. After completing an 8-week prospective Baseline Period, eligible subjects were randomized to receive placebo or BRV doses ranging from 5 mg/day to 100 mg/day (equally divided b.i.d. dosing) without up-titration during a 12-week Treatment Period. Analysis of covariance (ANCOVA) was applied to analyze log (x+1) transformed Treatment Period seizure frequency, with adjustment for stratification variables and log-transformed baseline

seizure frequency. Analyses were produced for POS frequency standardized to 7-day and 28-day durations. Treatment effects are characterized as percent reduction over placebo after back-transformation of effect estimates from the ANCOVA.

Results: Table 1 presents results for the ANCOVA analyses of POS frequency standardized to a 7-day and 28-day duration. The magnitudes of p-values are comparable for the two methods and conclusions regarding statistical significance are not altered. However, the effect estimates (percent reductions over placebo) differ for the two methods. The magnitude of effect estimates for the analysis of 7-day adjusted frequency appear to be inconsistent with secondary variables, such as median percent reduction in POS frequency from Baseline (Table 2). Furthermore, an evaluation of the underlying statistical methodology supports the conclusion that the analysis of 7-day adjusted seizure frequency underestimates the magnitude of the treatment effects, and the analysis of 28-day adjusted seizure frequency is statistically valid and provides effect estimates that more appropriately characterize the treatment effects for these studies.

Conclusions: These results illustrate the impact of the choice of statistical methodology on the perceived magnitude of treatment effect when applying a parametric statistical method to analyze log-transformed seizure outcome. The duration over which seizure frequencies are standardized may have a notable impact.

UCB-sponsored (NCT00464269; NCT00490035)

Table 1: Percent Reduction Over Placebo and Corresponding P-Values with Partial Onset Seizure Frequency Standardized to Alternative Durations (ITT Population)

IMAGE: tables/906492_T1.jpg

*Statistically significant at the 0.05 level

Number of ITT patients on placebo: N=100 (N01252) and N=96 (N01253).

NA=Not Applicable

Table 2: Median Percent Reduction in POS frequency per Week from Baseline to the Treatment Period (ITT Population)

IMAGE: tables/906492_T2.jpg

*Statistically significant at the 0.05 level

NA=Not Applicable

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UCB ANTIEPILEPTIC DRUG PREGNANCY REGISTRY-KEPPRA® DATA

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Rationale: The UCB Antiepileptic Drug Pregnancy Registry was created to advance scientific knowledge about safety and outcomes associated with use of UCB AEDs in pregnancy.

Methods: Enrollment in the US-based, observational, exposure-registration, prospective, follow-up registry is voluntary. The prevalence of birth defects is compared to prevalence in the Metropolitan Atlanta Congenital Defects Program, a population-based birth defects surveillance system administered by the Centers for Disease Control and Prevention. NCT00345475

Results: As of 28FEB2010, 428 women taking Keppra® (n=415), Keppra XR® (n=8) or both (n=5), were prospectively enrolled in the registry. Pregnancy outcomes were known for 385 women (387 fetal exposures), including 365 live births (two twin pregnancies), one induced abortion, three fetal deaths, and 18 spontaneous pregnancy losses. Total exposure data included 351, 30, and 6 first, second, and third trimester exposures, respectively. Birth defects were reported in 26 of 365 live births and in 1 fetal death.

Defects were reported in 12/253 (4.7%) live births following Keppra/Keppra XR monotherapy, including first trimester (10/227 exposed live births): peripheral pulmonary artery stenosis/patent foramen ovale, subaortic ventricular septal defect, bilateral club feet, pulmonary stenosis/dysplastic pulmonary valve, positional plagiocephaly/intermittent esophoria/flat feet, cleft lip, congenital torticollis/hydroceles, polydactyly/hemangioma, pyloric stenosis, and macrocephaly; second trimester (1/21 exposed live births): congenital nystagmus/scalp hemangioma; third trimester (1/5 exposed live births): congenital nevus/achrochordon/nevus simplex.

Defects were reported in 13/105 (12.4%) live births following Keppra/Keppra XR polytherapy without valproate, including first trimester (12/95 exposed lived births): congenital adrenal hyperplasia/Chiari I malformation (+phenytoin), facial asymmetry/hypertelorism/natal tooth/wide anterior fontanelle/hemangioma (+phenobarbital), ventricular septal defect/genu valgum (+oxcarbazepine and clonazepam), cleft palate/left eye ptosis (+carbamazepine), ectopic right kidney (+carbamazepine and phenytoin), membranous ventricular septal defect/atrial septal defect, hydronephrosis/posterior urethral valve, hypospadias, capillary hemangioma, hemangioma/right temporal dermoid cyst, omphalocele, 4th toe crosses under 3rd toe/hemangioma lower back (+ lamotrigine for all); second trimester (1/9 exposed live births): hypopigmentation fingers (+lamotrigine); third trimester (0/1 exposed live birth).

One case of hemangiomas was reported out of 7 live births following polytherapy with valproate (all first trimester exposures).

Finally, bilobed right lung/small mouth was identified in a stillbirth with first trimester exposure to Keppra and phenytoin.

Conclusions: The Expert Panel concluded that the limited amount of data currently available were insufficient to draw conclusions. The number of ventricular septal defects remains unchanged from the previous four reports. The Panel will update their assessment as more data become available.

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RETENTION RATE OF LACOSAMIDE IN COMPARISON TO OTHER NEWER ANTICONVULSANTS IN PATIENTS WITH EPILEPSY

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Rationale: Treatment of epilepsy often imposes an exposure to various anti-epileptic medications (AEDs) and requires long-term

commitment and compliance from the patient. With the advent of the newer generation of AEDs starting in the early 1990s, neurologists have gained a number of new AEDs to choose from. Two main considerations in selecting AEDs are their efficacy and tolerability, which are probably best evaluated by retention rate, defined as the percentage of patients remaining on the medication after a specified time period. We reviewed retention rate of newly approved AED, lacosamide (LCM), and compared to the previously published retention rate of other AEDs.

Methods: Retention data of LCM was obtained retrospectively by reviewing medical records in our epilepsy center at the Barrow Neurological Institute and interviewing patients if necessary. The data included patient's age, gender, seizure type, current and previous medications, dosage, main reasons for discontinuation, and duration of therapy. To avoid as much recall bias as possible, we also reviewed electronic records, as well as previous dictations to make sure that obtained data are credible and accurate. Patients who started LCM during phase II and III clinical trials were excluded, and patients who started LCM after being commercially available on June 3, 2009 were included in the study. In addition, patients were excluded if LCM was recently initiated within six months or less in order to access longer retention rates.

Results: Out of the total of 185 LCM exposures since June 3, 2009, 121 patients (53% female) were started LCM 6 months or longer for partial epilepsy treatment. LCM was initiated as an adjunctive therapy in all 121 patients. The overall retention rate of LCM was 79.34% (96 of 121) in six months. The interim retention rate at one month was 94.21%, and at three months, 85.95%. When compare to other AED retention rates in 6 months from the same clinic, LCM retention was better than levetiracetam (62.2%), oxcarbazepine (68.0%), topiramate (56.4%), or zonisamide (65.6%), but similar to that of lamotrigine (78.5%). When LCM was discontinued, it was mainly due to inefficacy (36%), dizziness (28%), and lethargy (24%) within 6 months of LCM therapy. Other reasons (<10%) of stopping LCM were due to diplopia (8%), irritability (8%), headaches (8%), financial limitations (8%), rash (4%), nausea (4%), weight gain (4%), and unknown reasons (4%).

Conclusions: Comparing retention rates of AEDs may provide useful insight into their tolerability and efficacy in epilepsy treatment. This study shows high retention rate of LCM at 6 months when compare to other newer AEDs at the same time frame. Beside ineffectiveness, leading causes of LCM discontinuation were dizziness and lethargy, although the overall incidence of these adverse effects was low (5.8% and 4.9% respectively).

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BIOEQUIVALENCE OF ORAL AND INTRAVENOUS CARBAMAZEPINE IN ADULT PATIENTS WITH EPILEPSY

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Rationale: Carbamazepine (CBZ) is a widely prescribed, oral antiepileptic drug approved in the United States and other countries. However, many patients are, on occasion, unable to take CBZ by mouth because of illness, injury, surgery, or changes in mental status. A new intravenous (IV) formulation (solubilized in a cyclodextrin matrix) is in clinical development, and a multicenter, sequential, open-label, Phase I study was conducted to assess the safety, tolerability, and comparative pharmacokinetics (PK) of IV and oral CBZ .

Methods: Adult patients with epilepsy stabilized on a fixed oral dosage of CBZ (400-2,000 mg/day) were converted to IV therapy, based on an estimated 70% mean bioavailability of oral CBZ. At the conclusion of a 28-day, outpatient lead-in period, patients arrived at a research unit on Day -1 already on oral CBZ maintenance therapy. The following day (Day 0), patients continued on oral therapy and had serial blood sampling to determine the area under the concentration-time curve (AUC) for CBZ and CBZ-10,11-epoxide (CBZ-E), the active metabolite, over 12 hours. IV CBZ infusions were then administered over 15 or 30 minutes every 6 hours for 7 consecutive days (Days 1-7). A group of patients also received four 2-5 minute infusions on Day 8 (following the 7 days of 15-minute infusions). On Days 1, 7, and 8, extensive blood sampling was conducted during the first 6-hour IV CBZ dosing interval, for measurements of plasma CBZ and CBZ-E concentrations. Safety assessments were conducted through Day 38.

Results: A total of 98 patients enrolled in the study. The mean daily oral CBZ dosage for 64 PK-evaluable patients with normal renal function was 962.5 mg, and the mean daily IV dosage was 675.1 mg (70% of the total daily oral dosage). PK data from these patients showed IV CBZ infused over 15 or 30 minutes or via 2-5 minute infusions led to C_{min} concentrations and overall exposure (AUC_{0-24}) of CBZ at steady state that were similar to those observed following oral CBZ at steady state (table). The 90% confidence intervals for the IV to oral CBZ ratios of geometric least-squares means (LSMs) for AUC_{0-24}, C_{max}, and C_{min} are also presented.

For plasma CBZ, IV CBZ infused over 30 minutes was bioequivalent to oral CBZ, as the 90% CIs for the ratios of the LSMs for AUC_{0-24}, C_{max}, and C_{min} were within the 80% to 125% range. For the 15-minute and 2-5 minute infusions, the 90% CI ratios of the LSMs for AUC_{0-24} and C_{min} were also within the 80% to 125% range. However, the 90% CI ratio of the LSM for C_{max} was greater than the upper limit of the 80% to 125% range.

Conclusions: IV carbamazepine infused over 30 minutes every 6 hours is bioequivalent to oral carbamazepine. Thirty-minute CBZ infusions given every 6 hours at a 70% dosage conversion from patients' oral dosages permitted patients to maintain their total CBZ exposures, as demonstrated by comparable IV and oral CBZ AUC and C_{min} parameters. C_{max} concentrations following 15-minute and 2-5 minute infusions transiently exceeded bioequivalence limits.

PK and Bioequivalence of IV and Oral CBZ in the Evaluable PK Population

IMAGE: tables/904336_T1.jpg

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ROLE OF THE MTOR INHIBITOR EVEROLIMUS IN TREATING PATIENTS WITH NEUROLOGICAL MANIFESTATIONS OF TUBEROUS SCLEROSIS COMPLEX (TSC): RATIONALE AND CURRENT CLINICAL TRIALS

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Rationale: TSC is a potentially devastating disorder characterized by hamartoma formation in multiple organ systems and associated disabling neurological disorders including epilepsy, mental retardation, and autism. TSC lesions occur throughout the body including the

kidney (angiomyolipomas), lungs (lymphangiomyomatosis), and brain (cortical tubers and subependymal giant-cell astrocytomas [SEGAs]). Epilepsy occurs in 80%-90% of patients with TSC, and seizures may be severe and often difficult to control with available antiepileptic drugs. The epileptogenic source is presumed to be neuronal tubers, cerebral cortex abnormalities present in 90% of patients with TSC. Neurosurgical resection, corpus callosotomy, and vagus nerve stimulation with their associated complications and comorbidities are the current standard treatments for intractable epilepsy associated with TSC; no effective alternatives have been identified. TSC is caused by mutations in 1 of 2 genes, *TSC1* or *TSC2*. The protein products of these genes, hamartin and tuberin, form a heterodimer to negatively regulate mTOR, a key intracellular kinase regulating cell growth and proliferation, cellular metabolism, and angiogenesis. Mutations in *TSC1* or *TSC2* result in constitutive mTOR activation that drives the pathogenesis of TSC. Currently there are no approved systemic therapies to treat the underlying cause of TSC (ie, unregulated mTOR activity).

Methods: Recently, an open-label, phase II trial (NCT00411619) of everolimus, an orally bioavailable, selective mTOR inhibitor, demonstrated a significant reduction in SEGA volume and a decreased frequency of seizures. Based on these promising efficacy data, additional phase II studies have been launched or are being planned to explore the benefit of everolimus in patients with neurological manifestations of TSC (Table). In addition, the ongoing EXIST-1 trial (**EX**amining everolimus **I**n a **S**tudy of **T**SC; NCT00789828), a randomized, prospective, double-blind, multicenter study, is the first placebo-controlled phase III study in patients with TSC.

Results: Everolimus has demonstrated promising efficacy in a phase II trial of patients with TSC.

Conclusions: Additional rationale supporting mTOR inhibition as a therapeutic target in patients with TSC and detailed study designs will be presented.

Key studies of everolimus in patients with neurological manifestations of TSC.

IMAGE: tables/907671_T1.jpg

SEGAs, subependymal giant-cell astrocytomas; TSC, tuberous sclerosis complex.

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EVALUATION OF THE RESPONSE TO ADJUNCTIVE PREGABALIN THERAPY BASED ON BASELINE SEIZURE RATE IN PATIENTS WITH REFRACTORY PARTIAL-ONSET EPILEPSY

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Rationale: 28-day baseline seizure rates vary within and among studies of pregabalin as adjunctive therapy for patients with refractory partial seizures. In all these studies, efficacy evaluations adjusted for baseline seizure variability; however, stratification of patients by baseline seizure rate was not feasible due to the size of the studies. The objective of this post hoc analysis was to evaluate the response to adjunctive pregabalin treatment based on the 28-day baseline seizure rate by pooling data from 6 similarly designed placebo-controlled studies of pregabalin in patients with refractory partial-onset seizures.

Methods: Data from 6 randomized, double-blind clinical studies of pregabalin in patients with refractory partial-onset epilepsy were pooled for this analysis. Patients received adjunctive treatment with 150, 300, or 600 mg/day pregabalin; flexible-dose pregabalin; or placebo in addition to e”1 concomitant antiepileptic drug. Patients were grouped according to their 28-day baseline seizure rate (d”5, >5 d”10, >10 d”23, >23) and response to pregabalin was analyzed using 50% Responder rate and RRatio. Responder rate was analyzed using logistic regression and RRatio by analysis of covariance with treatment as main effects and gender, age, duration since diagnosis, and baseline seizure rate as covariates.

Results: A total of 1775 patients (male, n=869 [48.9%]) who received placebo (n=566), 150 mg/day (n=185) 300 mg/day (n=242), 600 mg/day (n=532) or flexible-dose (n=250) pregabalin were pooled for this analysis. The mean (standard deviation) baseline seizure rate was 26.4 (144.8), 24.7 (38.8), 20.5 (34.4), 20.3 (34.5) and 44.5 (443.0) for placebo, 150 mg/d, 300 mg/d, 600 mg/d, and flexible-dose pregabalin, respectively. Significant improvements in Responder rates were observed across all baseline seizure rates for 600 mg/day (odds ratio [OR] range: 5.7-7.9; P<0.0001) and flexible-dose (OR range: 2.5-3.5; P<0.05) pregabalin versus placebo. Significant benefits were also observed for 600 mg/day and flexible-dose pregabalin for least squares mean (LSM) difference in RRatio (range, -15.4 to -33.9; Pd”0.014) across all baseline seizure cut-offs, except for nonsignificant improvements for a baseline seizure rate of >10d”23 (LSM difference, -8.7; P=0.237) in the flexible-dose group. Additionally, 150 and 300 mg/day pregabalin improved both the Responder rate (OR, 150 mg/d: 3.2 and 300 mg/d: 4.1; P<0.02) and RRatio (LSM difference, 150 mg/d: -20.7; 300 mg/d: 25.7; P<0.01) in patients with a baseline seizure rate of d”5.

Conclusions: Higher pregabalin doses (eg, 600 mg/day) consistently improved both Responder rate and RRatio regardless of baseline seizure rate, while lower (eg, 150 and 300 mg/day) pregabalin doses provided seizure reductions on both measures at lower baseline seizure rates. This study suggests that seizure reduction with pregabalin may be dependent on both dose and baseline seizure rate in patients with refractory partial seizures. Funded by Pfizer.

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IMPROVED SEIZURE SEVERITY, HEALTH-RELATED QUALITY OF LIFE AND HEALTH STATUS REPORTED BY PATIENTS DURING LONG-TERM TREATMENT WITH LACOSAMIDE

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Rationale: Lacosamide is a new AED for adjunctive treatment of partial-onset seizures in adults. For the first time, the effects of long-term lacosamide treatment on patients’ self-reported seizure severity, health-related quality of life (HRQoL), and health status are reported.

Methods: In the phase 3 open-label extension trial SP756 (NCT00522275), the Seizure Severity Questionnaire (SSQ; Cramer, 2002), Quality of Life In Epilepsy scale (QOLIE-31; Cramer, 1998), and Patient Global Impression of Change (PGIC) were included as health-outcomes assessments. The SSQ, measuring seizure severity on a 7-point scale, and the QOLIE-31, an epilepsy-specific HRQoL assessment with a 100-point range, were completed at weeks 16 and 48, with subsequent assessments every 48 weeks. The PGIC, a 7-

category scale assessing change in health state, was performed at weeks 16 and 48. SSQ and QOLIE-31 scores at week 48 were compared to baseline scores in the double-blind trial that lead into the open-label trial. Data were analyzed using t-tests for observed cases (scores at each visit for patients with data at that visit), as well as a last observation carried forward approach (LOCF). The percentage of patients with a clinically meaningful QOLIE-31 improvement, based upon thresholds previously defined by the authors using phase 3 lacosamide trial data, was described at week 48. The percentage of patients by PGIC category was also described.

Results: At week 48 (LOCF, n=270), patients showed a significant mean improvement on all SSQ subscales, including cognitive, emotional and physical effects during and after seizures. Patients also showed an average improvement of -0.64 on the Overall SSQ score, a rating combining overall seizure severity and bother. Improvement on all QOLIE-31 subscales was shown with the exception of Medication Effects (-1.85, NS). Significant improvements were found for Seizure Worry (+9.00), Quality of Life (+3.86), Emotional Well-Being (+2.38), Social Functioning (+3.43), and the Total score (+2.89). On average, QOLIE-31 scores showed additional improvement after the first year. For all QOLIE-31 subscales, more than 35% of patients showed clinically meaningful improvement at week 48. The largest percentages of improved patients were found for the subscales of Seizure Worry (49.2%) and Social Functioning (50.8%). On the PGIC, 79.5% of patients reported overall improvement at week 16 (n=283), with 53.0% of patients in the very much or much improved category. At week 48 (n=244), 79.1% of patients said to have improved overall, with 64.3% of patients in the very much or much improved category.

Conclusions: After one year of lacosamide treatment, significant improvements in all aspects of seizure severity, as well as in most aspects of HRQoL were observed. About half of patients showed clinically meaningful improvement on seizure worry and social functioning, indicating the effectiveness of lacosamide for both seizures and health-related outcomes. Most patients reported their overall health state to be much or very much improved.

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LONG-TERM EFFICACY OF LACOSAMIDE AS ADJUNCTIVE THERAPY IN PATIENTS WITH UNCONTROLLED POS: RESULTS FROM A PHASE III OPEN-LABEL EXTENSION TRIAL

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Rationale: Lacosamide is an antiepileptic drug (AED) approved for the adjunctive treatment of partial-onset seizures. In a previously completed Phase III double-blind, randomized trial (SP754; NCT00136019; Chung *et al., Epilepsia* 2010), treatment with adjunctive lacosamide significantly reduced the frequency of partial-onset seizures. We report final efficacy results for the subsequent open-label extension (OLE) trial (SP756; NCT00522275) with lacosamide exposure through 5 years.

Methods: Patients completing the maintenance phase of the US Phase III double-blind clinical trial (Chung *et al., Epilepsia* 2010), who elected to enter the OLE trial were transitioned to a lacosamide dose of 200 mg/day. Lacosamide could be decreased to 100 mg/day or increased up to 800 mg/day (in 100 mg/day per week increments), and concomitant medications could be increased or decreased on an individual basis. Safety evaluation during long-term exposure was the primary objective of the trial (results reported separately); efficacy endpoints included percent change in 28-day partial seizure frequency, responder rate (percentage of patients with a e”50% or a e”75% reduction in partial seizure frequency from Baseline of the previous trial); and seizure-free status for yearly completer cohorts. Data were analyzed for those patients receiving at least one dose of open-label lacosamide with at least one post-Baseline efficacy assessment.

Results: A total of 308 patients were exposed to lacosamide in this OLE trial. Of these, 307 had post-Baseline efficacy data available. The median modal dose of lacosamide (patient modal dose = the dose the patient used most often during the trial) was 500 mg/day, and 39% of patients had a modal dose e”600 mg/day. Median treatment duration was 1075 days. Most patients (82%) were receiving 2-3 concomitant AEDs at Baseline of the previous trial, and 50% had tried 7 or more lifetime AEDs. The e”50% and e”75% responder rates were 48.2% and 24.4% for the entire treatment period; responder rates increased over time for patients completing each time point. Of those patients exposed to lacosamide for at least 2 years, 6/193 (3.1%) remained seizure free from the first dose of open-label lacosamide through at least 2 years.

Conclusions: Long-term treatment with lacosamide in this open-label study was associated with a reduction in seizures and maintenance of efficacy.

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POPULATION PHARMACOKINETICS AND PHARMACODYNAMICS OF PERAMPANEL IN PATIENTS WITH REFRACTORY PARTIAL SEIZURES

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Rationale: RATIONALE: Perampanel (E2007) is a highly selective alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonist currently in development as adjunctive therapy for patients with refractory partial seizures. This population pharmacokinetic (PK)/pharmacodynamic (PD) analysis describes the PK of perampanel and the relationships between (a) exposure and seizure frequency and (b) exposure and central nervous system (CNS) adverse events (AEs).

Methods: In 2 double-blind, placebo-controlled, Phase II studies, adult patients with refractory partial-onset seizures receiving d”3 concomitant antiepileptic drugs (AEDs) were randomized to receive either placebo or adjunctive oral perampanel (Study 1: 1-4 mg/d [QD or divided doses BID], 8-week titration, 4-week maintenance; Study 2: 2-12 mg QD, 12-week titration, 4-week maintenance). Plasma samples taken every 2 weeks during titration and once at the end of maintenance, down-titration, and last visit (Study 1) or at the end of titration and maintenance (Study 2) were analyzed for perampanel using a validated method. Population PK (POPPK) and exposure-response parameters were estimated using non-linear mixed-effect modeling. Patient average perampanel steady-state concentrations were derived from a POPPK model and related to 28-day seizure frequency at scheduled assessment visits (exposure/efficacy analysis) and to the daily occurrence of CNS AEs (exposure/safety analysis). Logistic regression (SAS) was used to analyze the probability of the occurrence of CNS AEs in relation to exposure and other covariates.

Results: 176 patients were included in the population PK analysis (median age 42 years, 55% female, 89% Caucasian). Perampanel plasma concentrations were adequately described by a one-compartment disposition model with first-order absorption and elimination. Inter-

individual variability was estimated for apparent clearance (CL/F) and apparent volume of distribution (V/F). Overall, perampanel CL/F was 1.33 L/h decreasing slightly from first dose to 1.02 L/h following 20 weeks of treatment and exposure was approximately 2-fold lower in patients co-administered with other AEDs that are strong CYP450 inducers, compared to patients not receiving inducers. PK/PD analyses described a concentration-dependent decrease in 28-day seizure frequency and increased probability of response (50% reduction in seizure frequency from baseline) relative to placebo. Occurrence of CNS AEs increased with perampanel exposure.

Conclusions: Perampanel PK can be described by a one-compartment model with first-order disposition. Co-administration of other AEDs that are strong CYP450 inducers decreased exposure to perampanel. Data in this study confirm that perampanel provides concentration-dependent decreases in seizure frequency when co-administered with other AEDs. Based on the results of this study and other studies, 3 Phase III studies and their extension study have commenced and are ongoing.

(Support: Eisai Inc)

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LONG-TERM SAFETY OF LACOSAMIDE AS ADJUNCTIVE THERAPY IN PATIENTS WITH UNCONTROLLED PARTIAL-ONSET SEIZURES: RESULTS FROM A PHASE III OPEN-LABEL EXTENSION TRIAL

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Rationale: As the pharmacological management of epilepsy often requires long-term treatment with antiepileptic drugs (AEDs), it is necessary to examine the safety of AEDs upon prolonged exposure. The short-term safety and efficacy of the AED lacosamide for adjunctive treatment of partial-onset seizures has been established in three Phase 2/3 double-blind, placebo-controlled trials. The primary goal of this Phase 3 multicenter, uncontrolled open-label extension (OLE) trial (SP756; NCT00522275) was to examine the long-term safety of lacosamide in patients exposed for up to 5 years.

Methods: Patients completing the maintenance phase of the US Phase 3 double-blind clinical trial (SP754; NCT00136019; Chung *et al., Epilepsia* 2010), who elected to enter the open-label extension trial were transitioned to a lacosamide dose of 200 mg/day to begin open-label treatment. This dose could be adjusted as necessary up to a maximum of 800 mg/day (in 100 mg/day per week increments) or decreased to a minimum of 100 mg/day; concomitant AEDs could also be increased or decreased on an individual basis. The safety outcomes included: adverse events (AEs), serious AEs (SAEs), withdrawal due to AEs, and changes in hematology, blood chemistry, urinalysis parameters, 12-lead ECGs, vital signs, body weight, and physical or neurological examination findings. Data were analyzed for all patients who received at least one dose of open-label lacosamide.

Results: A total of 308 patients were exposed to open-label lacosamide (median modal dose 500 mg/day) over the trial period, representing 767.4 patient-years exposure. A total of 75% of patients completed at least 12 months of open-label treatment. Of the 138 (45%) patients remaining at trial closure (following commercial availability of lacosamide), 128 (93%) continued lacosamide as part of their post-trial treatment regimen. The primary reasons for trial withdrawal were lack of efficacy (26%) and AEs (11%). The most common treatment-emergent AEs (e”15%) occurring at anytime over the duration of the trial included dizziness (50.0%), headache (21.8%), contusion (18.5%), nausea (18.5%), convulsion (17.2%), nasopharyngitis (17.2%), fall (15.9%), vomiting (15.9%), and diplopia (15.3%). The incidences of treatment-emergent AEs that led to discontinuation in e”1.0% of patients were dizziness (1.6%) and convulsion (1.0%). A total of 71 (23%) patients reported an SAE, the most common (>1.0%) being convulsion (3.6%), chest pain (1.6%), pneumonia (1.6%), dizziness (1.3%), and vomiting (1.3%). There was no meaningful pattern of changes from baseline of the previous trial in hematology, blood chemistry, urinalysis, ECG parameters, vital signs, body weight, or physical/neurological exam findings.

Conclusions: Long-term, open-label adjunctive treatment with lacosamide up to 800mg/day was generally well tolerated in this trial of patients with refractory partial-onset seizures. The safety profile was consistent with that of other clinical trials with lacosamide.

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RUFINAMIDE FOR REFRACTORY EPILEPSY IN A PEDIATRIC AND YOUNG ADULT POPULATION

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Rationale: Rufinamide is a new antiepileptic drug recently approved by the FDA as an adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS). It has a few specific attributes that make it an attractive option for an AED: few serious side effects, few drug interactions, and quick titration. To further extend the clinical knowledge of this new drug, the present chart review study was conducted to further examine the safety and efficacy of rufinamide adjunctive therapy in pediatric and young adult patients with a variety of seizure types.

Methods: This chart review study included male and female pediatric and young adult patients receiving rufinamide for epilepsy between January and November 2009 at the Blue Bird Circle Clinic for Pediatric Neurology at Texas Children’s Hospital, a comprehensive epilepsy center. Patients were regularly evaluated for seizure response and adverse events and classified according to subjective reports and seizure diaries. Responders were defined as patients who had a 50% or greater decrease in seizure frequency, with significant response defined as a 75% or greater decrease in seizure frequency.

Results: Charts for 45 patients (26 M, 19 F) were reviewed. Mean patient age at the time of review was 9.5 years. 44 patients (97.8%) had received previous therapy with 1 or more AEDs (range, 0-9) prior to starting rufinamide. 43 patients (95.6%) were receiving concurrent AED drug therapy (mean AEDs 2.14, range, 0-4). Mean rufinamide dosage was 827.3 mg/day, or 30.1 mg/kg/day (range, 300-1800 mg/day or 6.7-57 mg/kg/day). Mean duration of rufinamide therapy was 21 weeks (range, 1-103 weeks). Patients experienced a broad spectrum of partial and generalized seizure/epilepsy types. 19 patients (46%) were determined to be responders, and 22 patients (54%) were non-responders. Of the non-responders, 15 patients (68%) stopped due to lack of efficacy, 5 patients (23%) stopped due to an increase in seizure frequency, and 2 patients (9%) stopped due to adverse effects. Of the patients who responded to therapy, 7 patients (37%) were classified to have significant response to rufinamide therapy, and 12 patients (63%) had mild-moderate responses. 17 patients (37.8%) stopped their trial of rufinamide prior to the end of the review period.

Conclusions: The results of our study indicate that rufinamide is a helpful adjunct in the therapy of a variety of refractory seizure types both in children and in young adults. This is consistent with data from previous studies. 46% of our patients exhibited a reduction in seizure frequency, with 37% of the responders showing a more than 50% decline in seizure frequency. Rufinamide appeared to have had a relatively good safety profile, as only two patients stopped the medication due to adverse effects. However, 15 patients did not think that the medication helped them, and 5 actually had an increase in seizure frequency on rufinamide. Allowing for the limitation of small sample size and the retrospective nature of the study, our data shows promise that rufinamide therapy may be a relatively safe adjunct in the treatment of refractory epilepsy.

IMAGE: images/886160_A.jpg

1.267

ADJUNCTIVE BRIVARACETAM IN ADULTS WITH UNCONTROLLED GENERALIZED SEIZURES: SUB-POPULATION ANALYSIS OF THE RESULTS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Rationale: Brivaracetam (BRV), a novel high-affinity SV2A ligand with inhibitory activity on neuronal voltage-dependent sodium channels, has demonstrated efficacy against partial-onset seizures in phase 2 clinical trials. Data from preclinical studies suggest BRV may have a broad spectrum of clinical activity. To explore its tolerability and efficacy against generalized seizures (GS), we analyzed a sub-population of a phase 3 clinical trial, focusing on patients with GS only and diagnosis of generalized epilepsy (GE).

Methods: The prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose trial (N01254/NCT00504881) randomized (BRV:Placebo 3:1) adults (16-70 years) experiencing uncontrolled focal seizures or GS, despite treatment with 1-3 AEDs. The proportion of patients with GS was limited to 20%. Patients with GE had to experience e”2 GS days/month for 3 months prior to screening and e”4 GS days during the 4-week prospective Baseline. The Treatment Period comprised an 8-week Dose-finding and 8-week Maintenance. BRV was initiated at 20 mg/day and increased stepwise (50, 100 and 150 mg/day, bid) at the investigator’s discretion.

Results: Of 480 patients randomized to treatment, 49 (10.2%) presented with GE (36 BRV; 13 placebo; mean age:30 years; 53% male). Syndrome classification was idiopathic in 27/49 (55%), cryptogenic in 14/49 (29%), symptomatic in 4/49 (8%) and unknown in 4/49 (8%) patients. Patients were on 1 (29%), 2 (41%) or e”3 (29%) concomitant AEDs, the most common of which were lamotrigine (33%), carbamazepine (29%) and valproate (25%). During Baseline, patients experienced tonic-clonic (59%), absence (37%), tonic (14%), myoclonic (10%), clonic (6%) and atonic (4%) seizures. 34/36 (94.4%) BRV and 13/13 (100%) placebo patients completed the Treatment Period, during which similar proportions (72.2% and 76.9%, respectively) reported e”1 treatment emergent adverse event (TEAE); the majority of which were mild to moderate. The most frequently reported TEAEs (e”10% patients; either group) were headache (BRV 7/36, 19.4%; placebo 4/13, 30.8%), somnolence (BRV 4/36, 11.1%; placebo 0/13, 0%) and mouth injury (BRV 0/36, 0%; placebo 2/13, 15.4%). Only one patient on BRV (1/36, 2.8%) discontinued treatment because of TEAE. The median baseline GS days/week was similar in both groups (BRV 1.42; placebo 1.47). Exploratory efficacy analysis showed that during the Treatment Period the median GS days/week decreased to 0.63 on BRV and remained relatively stable on placebo (1.26). The median percentage reduction from baseline and 50% responder rate in GS days/week were higher on BRV (42.6% and 44.4%, respectively) compared with placebo (20.7% and 15.4%, respectively). 3 (8.3%) patients on BRV were seizure free during the entire Treatment Period compared with none on placebo.

Conclusions: The results of this exploratory analysis provide preliminary data suggesting potential efficacy and good tolerability of adjunctive BRV in adults with GE.

UCB-sponsored

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INTRAVENOUS LACOSAMIDE IN REFRACTORY STATUS EPILEPTICUS AND SEIZURE AGGRAVATION

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Rationale: Status epilepticus (SE) and seizure clusters represent neurological emergencies. The mortality rate for adults ranges from 11% to 34%, depending on cause and co-morbidity (Delorenzo et al., 1996). As SE become more refractory to treatment over time, rapid, appropriate treatment is of particular importance.

This study aimed to investigate the effectiveness and tolerability of IV lacosamide (LCM) in treatment of seizure clusters and SE after failure of first line treatment benzodiazepines.

Methods: All patients treated with IV LCM between December 2009 and January 2010 were retrospectively enrolled in our study. We analyzed indications for treatment, dose, responsiveness and adverse events.

Indications for IV LCM were (1) previously unsuccessfully treated SE or (2) seizure clusters triggered by antiepileptic drug (AED) reduction during video-EEG monitoring due to rapid down titration.

Results: Nineteen consecutive patients (12f/7m) aged 20-91 years (median 53 years) were included in the study. Six patients had convulsive SE, three patients nonconvulsive SE and ten patients had seizure clustering. The atiology of epilepsy was in 6/19 traumatic laesions, in 5/19 cortical dysplasia, in 4/19 vascular laesions, in 2/19 cryptogenic, in 1/19 vitamin B-hypovitaminosis and in 1/19 an aluminium intoxication. The initial dosis was mean 257.9 mg (SD 90.2), median 200 mg (range 200-400). The rate of infusion in patients with SE ranged between 40 - 57mg/min, in patients with seizure clusters 20 - 57mg/min. LCM IV was used as third drug.

Nonconvulsive SE was terminated with LCM IV in 3/3 patients, convulsive SE in 1/6 patients and in 8/10 patients with seizure clusters

LCM IV was effective. Except pruritus in one patient no side-effects were observed, especially no cardiovascular effects were observed.

Conclusions: These data support consideration of LCM IV use as a safe alternative to standard AED therapies for acute treatment of seizure emergency situations. Further studies on optimal dose, rate of infusion efficacy and safety are needed.

(1) Delorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, Garnett L, Fortner CA, Ko D. (1996) A prospective, population- based epidemiologic study of status epilepti- cus in Richmond, Virginia. Neurology 46: 1029-35.

1.269

BIOEQUIVALENCE OF A CAPTISOL-ENABLED®FOSPHENYTOIN SODIUM INJECTION FORMULATION TO THE MARKETED REFERENCE LISTED PRODUCT VIA IV AND IM ADMINISTRATION IN HEALTHY VOLUNTEERS

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Rationale: A new formulation of fosphenytoin sodium has been developed by CyDex Pharmaceuticals, Inc., to provide enhanced stability and room temperature storage of the drug product. This will allow broader use by emergency personnel and more rapid access to therapy in most situations. The new formulation contains the solubilizing agent, Captisol, a substituted cyclodextrin known to form reversible complexes with phenytoin and to a much lesser extent fosphenytoin. It is critical to understand any effects that the presence of the cyclodextrin might have on therapy so intravenous (IV) and intramuscular (IM) bioavailability (BA) studies were conducted in healthy volunteers comparing the new formulation, Captisol-Enabled Fosphenytoin Sodium (CE-FOS), to equivalent doses of the commercially available reference product, Cerebyx® (Parke-Davis). In addition, safety and tolerability of the two formulations was evaluated.

Methods: The studies used a single-dose, double-blind, randomized, two-period crossover design with IM doses of 1000 mg PE (phenytoin equivalents) per injection site and IV doses of 10 mg PE/kg infused at 150 mg PE/minute (300 mg/min Captisol). Blood samples were taken over 48h and analyzed for total phenytoin (total and non-protein bound for the IV study) using a validated LC/MS/MS method with isotopic phenytoin-D10 internal standard.

Safety monitoring included analysis of 24-hour urine collections obtained prior to, immediately after, and 14 days following IV injection of the test products. The study was conducted at CEDRA Corporation (Austin, Texas).

Pharmacokinetic (PK) parameters for phenytoin were calculated using non-compartmental analysis. Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, Cmax and AUC. The 90% confidence intervals for the ratio of the geometric means (Test/Reference) were calculated and bioequivalence declared if the lower and upper confidence intervals were within 80% to 125%.

Results: PK analysis was conducted on 34 of 38, and 50 of 52 subjects completing the IV and IM studies respectively. Results for total phenytoin are presented in Table 1.

The 90% confidence interval for comparing ln(Cmax), ln(AUClast) and ln(AUCinf) were determined to be within the accepted 80% to125% limits for both routes of administration.

There were no changes in urinary excretion of monitored analytes other than a small increase in urinary chloride and sodium during the first day following administration of the test drugs.

Conclusions: CE-FOS is bioequivalent to the Cerebyx formulation following both IV and IM administration, and shows a similar safety profile. This new Room-Temperature stable formulation will allow broader use of fosphenytoin, particularly in the field and emergency situation.

Table 1. PK parameters for total phenytoin*

IMAGE: tables/907297_T1.jpg

*Data are Mean ± SD (standard deviation)

1.270

FIRST OBSERVATIONS OF RUFINAMIDE IN CHILDREN WITH MYOCLONIC-ASTATIC EPILEPSY

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Rationale: We report about the add-on therapy of the orphan-drug rufinamide (RUF), which is licensed for Lennox-Gastaut-Syndrome in six patients with difficult-to-treat Doose-Syndrome (= myoclonic-astatic epilepsy, MAE).

Methods: Patients and Methods:

Six Patients (4 male; age 4 to 20 years, mean age 6 2/12 years) with MAE were included in a retrospective evaluation of treatment with RUF. All patients had difficult-to-treat epilepsy- average anticonvulsive pre-treatment was nine anticonvulsive drugs (AED) (range 2- 14 AED; mean 7), together with mild to severe mental retardation (five mild; one severe). RUF was gradually introduced as add-on therapy.

Responder were defined as a reduction of seizure frequency >50% in comparison to four weeks before starting the therapy with RUF and a lasting effect for at least three month (RS).

Results: Responders were five of six patients (83.3%), one patient became seizure-free, four patients showed a 75 % reduction of seizure frequency. The best effect of RUF was noticed for drop-attacks, generalized tonic-clonic seizures and tonic seizures. After RUF treatment for six month we had four responders out of the six patients (66.6%); after 12 month four patients of five (80%) still showed a 75% reduction of seizure frequency and after 18 month one patient out of three (33%) still taking RUF reported a 80 % reduction of his main seizure types drop-attacks and myoclonic seizures.

Side-effects (SE) occurred in 40 % and were mainly decreased appetite and sleepiness which got less after the patient had become accustomed to the medication; no aggravation of seizures was seen.

Conclusions: In a small number of patients with refractory MAE we observed a high efficacy with RUF (an orphan drug for LGS). Some

loss of efficacy was noticed in the long-term treatment. Further multicenter studies a warranted to confirm our first observations.

1.271

A CLINICAL STUDY OF THE EFFECT OF ICA-105665 ON PHOTIC-INDUCED PAROXYSMAL EEG RESPONSES

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Rationale: Seizures can occur as a reaction to flickering light in patients with photosensitive epilepsy. Photoparyoxysmal EEG responses (PPR) to intermittent photic stimulation (IPS) can be studied in the laboratory without eliciting clinical seizures, and sensitivity to IPS can be used as a quantitative indicator of antiepileptic drug (AED) activity. In these studies, the standard photosensitivity range (SPR) is defined by the lowest and highest threshold frequencies of IPS eliciting a PPR. Narrowing or abolishing the SPR indicates anti-seizure activity. ICA-105665 is a novel molecule that opens neuronal KCNQ potassium channels and has demonstrated anti-seizure activity in multiple animal models. In prior Phase I studies, healthy volunteers and patients with epilepsy tolerated ICA-105665 in single doses up to 400 mg and multiple doses up to 200 mg BID for 7 days without dose-limiting side effects. The pharmacodynamic effects of increasing oral doses of ICA-105665 on the SPR were investigated in a placebo-controlled study in patients with photosensitive epilepsy. To our knowledge, this is the first study of the effects of a KCNQ opener on the PPR.

Methods: Male and female patients aged 18 to 60 years with a reproducible IPS-induced PPR on EEG were eligible for enrollment. The study was conducted as a single-blind, single dose, multiple cohort study. Four patients were enrolled in each of the first 3 cohorts. Patients could participate in more than one cohort. PPR responses to IPS were used to determine the SPR following placebo and ICA-105665. The SPR was quantified for 3 eye conditions (eyes closing, eyes closed, and eyes open) and the most sensitive condition used for assessment of efficacy over 3 days. A partial response was defined as a reduction in the SPR of at least 3 units at 3 separate time points following ICA-105665 compared to the same time points following placebo with no time points with > 3 units of increase. Complete suppression was defined by no PPR in all eye conditions at one or more time points.

Results: Six individual patients participated in the first 3 cohorts (100 mg, 200 mg and 400 mg). Decreases in SPR occurred in 1 patient at 100 mg and 2 patients receiving 400 mg ICA-105665 (complete abolishment of SPR occurred in 1 patient at 400 mg). The SPR remained diminished for 24 hours after dosing in 1 patient. All AEs were mild in severity, and there were no serious AEs. No patient discontinued study participation because of an AE. There were no significant changes in vital signs or clinical laboratory studies.

Conclusions: ICA-105665 reduced the SPR in some patients at single 100 and 400 mg doses. Based on the results in patients with photosensitive epilepsy, ICA-105665 should be assessed for anti-seizure activity in additional clinical studies of patients with other seizure types.

1.272

PHARMACOLOGICAL EFFECTS OF RETIGABINE ON BLADDER FUNCTION: RESULTS FROM PATIENTS IN PHASE 2/3 STUDIES

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Rationale: Retigabine (RTG; ezogabine in North America) is a first-in-class AED that reduces neuronal excitability by enhancing the activity of KCNQ (Kv7) K+ channels. In preclinical toxicology studies, RTG was shown to inhibit urinary bladder contraction, with these effects considered the result of a direct pharmacological effect at additional KCNQ channels, potentially KCNQ5 or KCNQ3/4, expressed in urinary bladder smooth muscle. These preclinical findings have been extensively evaluated in the clinical program. Here we summarize the safety profile of RTG associated with bladder function from an integrated dataset of Phase 2 and 3 clinical studies (data as of October 2, 2009).

Methods: Renal/urinary safety was assessed in RTG-treated patients from 5 completed Phase 2 (Studies 200/201, 202, 205, 209, and 214), 2 completed Phase 3 (RESTORE 1/Study 301 [NCT00232596] and RESTORE 2/Study 302 [NCT00235755]), 4 completed long-term open-label extension (LTOLE; Studies 208, 212, 216, and 8017), and 2 ongoing LTOLE (Studies 303 [NCT00310375] and 304 [NCT00310388]) studies. Safety evaluations of bladder function included adverse events (AEs) related to urinary retention/voiding dysfunction, assessments of American Urological Association Symptom Index (AUA SI) scores and postvoid residual (PVR) volume.

Results: A total of 1365 patients were exposed to RTG (most at 900 to <1200 mg/day), with a median total exposure of 261 days. Voiding dysfunction and urinary retention-related AEs were reported by 118 (8.6%) patients, including urinary hesitation (3.1%), urinary retention (1.9%), and residual urine volume (1.2%). Serious AEs of urinary retention were reported by 4 patients and 5 patients required urinary bladder catheterization. Urinary hesitation and retention led to discontinuation in 1 (<0.1%) and 6 (0.4%) patients, respectively. Urinary symptoms generally remitted following discontinuation of RTG, suggesting reversibility consistent with a pharmacological effect. To put these data in context, the incidences of urinary hesitation, urinary retention, and residual urine volume in placebo-treated patients in the Phase 2/3 randomized controlled trials (n=427) were 0.9% (4 patients), 0.5% (2 patients), and 0.2% (1 patient), respectively. AUA SI scores generally remained consistent and low (d”7: mild). PVR values of potential clinical concern were reported by 55 of 642 (9%) evaluable patients, 9 for whom PVR values were of concern at baseline.

Conclusions: RTG can exert a pharmacological effect on bladder function as evidenced by voiding dysfunction and urinary retention-related AEs and, in those patients evaluated, a slight but reversible increase in PVR volume. Importantly, the majority of these AEs were mild with most patients able to continue treatment without difficulties. However, caution should be taken in patients at risk of urinary retention. While RTG may affect human bladder function leading to urinary retention in a small number of patients, the data do not suggest an irreversible effect of RTG on bladder function.

Funded by Valeant Pharmaceuticals International and GlaxoSmithKline.

1.273

SIDE EFFECTS AND TOLERABILITY OF IV LEVETIRACETAM VS. IV PHENYTOIN AND FOLLOW-ON ORAL REGIMENS IN A NEUROSURGICAL PATIENT POPULATION: A PROSPECTIVE RANDOMISED STUDY

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Rationale: Intravenous (IV) levetiracetam (LEV) is an effective antiepileptic drug (AED) with potential to be particularly useful where IV phenytoin (PHY) is contraindicated or not tolerated. We aimed to compare the side effect profile including tolerability of IV LEV and IV PHY and follow-on oral regimens for seizure prophylaxis amongst a neurosurgical patient population.

Methods: Study design was single-centre, prospective, block-randomised, and researcher-blinded. Participants received at least one standard dose of IV LEV or IV PHY peri-operatively, then the same oral AED. Side effect profile, medication continuation, and seizure number, were recorded two days post IV administration, at hospital discharge, and three months following surgery, and compared between the AED regimens.

Results: 74 participants were randomised. Two-day (two-day to discharge, discharge to 3 month) datasets were complete for 36 (34, 25) LEV and 36 (35, 18) PHY participants. 81% (82%, 56%) LEV vs. 86% (89%, 72%) PHY recorded no systemic side effects [p=0.38 (0.35, 0.22)]; 3% (3%, 4%) LEV vs. 6% (3%, 17%) PHY recorded major systemic side effects [p=0.50 (p=0.51, 0.19)]; line-site complication was recorded only in the PHY group (6% [p=0.25]); 0% (0%, 4%) LEV vs. 3% (3%, 28%) PHY ceased medication because of AED side effects [p=0.50 (0.51, 0.04)]; seizures occurred in 3% (3%, 0%) of patients taking PHY, and none taking LEV [p=0.50 (0.51, 1.0)].

Conclusions: IV LEV and IV PHY are well tolerated peri-operatively. Oral LEV was better tolerated at 3 months. Lower than expected local side effect frequency for IV PHY may reflect anaesthetist technique.

1.274

PERAMPANEL RANDOMIZED CONTROLLED TRIALS IN EPILEPSY: A GLOBAL PHASE III PROGRAM

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Rationale: Perampanel is a novel AMPA antagonist, in development for epilepsy by Eisai Inc. A worldwide development program is needed to understand and prescribe new drugs appropriately. Broad patient demographics, including full representation of concomitant AEDs are needed. It is important to consider PK/PD and dose/response data on perampanel co-administered with CYP3A4 inducing/non-inducing AEDs, obtained from Phase II trials, to select appropriate doses toward optimally designed Phase III trials.

Two identical, randomized, placebo-controlled Phase III trials have been undertaken (EXPLORE 304 and 305) to assess safety and efficacy of perampanel (8mg, 12mg) in patients with treatment-resistant partial-onset seizures. Pop-PK and exposure-response are evaluated with the sparse PK sampling approach to plasma concentrations of perampanel and concomitant AEDs. These trials are being conducted in different regions of the world.

Methods: As of May 2010, EXPLORE 305 had enrolled 315/449 (70%) patients from 78 sites in Europe/Israel, the United States, India/S. Africa (after screen failures and early terminations). EXPLORE 304 had similarly enrolled 364/534 (68%) patients from 77 sites in S. America/Mexico, and N. America. Patient characteristics including age, gender, number of background AEDs (1, 2 or 3), and use of hepatic enzyme-inducing AEDs at baseline were compared among subjects for different regions and countries. Only countries randomizing >20 subjects were used for individual country assessment. Type of AED was evaluated using an earlier and smaller clinical dataset (EXPLORE 305 n=271; EXPLORE 304 n=310).

Results: Age and gender of subjects did not differ by region, but race varied regionally mainly in percentages of Caucasians and Asians. Mean number of background AEDs among subjects in different countries was similar, from 2.0 (Mexico, Chile) to 2.5 (Israel). Use of a single background AED ranged from 4-5% (Canada, Israel) to 21% (Mexico). Only in Israel were most subjects (59%) on 3 AEDs. Regional use of inducers as background AEDs averaged 58% but varied. Use of the 4 older AEDs: carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB) and valproic acid (VAL) was higher in S. America/Mexico and India/S. Africa, and lower in N. America and Europe/Israel (see table). Conversely, the newer AEDs lamotrigine (LTG) and levetiracetam (LEV) were used more in N. America and Europe/Israel.

Conclusions: The global perampanel Phase III program was based on Phase II results in subjects exposed to a broad range of doses and concomitant inducer/non-inducer AEDs. PK/PD analysis and dose/response outcome were used to conclude that no dose adjustments would be needed to assess efficacy outcomes and to select appropriate doses for Phase III. The Phase III program, with broad demographic representation of subjects on a full range of concomitant inducer/non-inducer AEDs, with the differences shown here in background AEDs across regions, will allow assessment of PK/PD interactions, which is helpful for accurate and useful prescribing information.

(Support: Eisai Inc.)

IMAGE: tables/906781_T1.jpg

1.275

THE RELATIONSHIP BETWEEN MOOD SYMPTOMS AND BASELINE SEIZURE RATE AND RESPONSE TO PREGABALIN IN PATIENTS WITH REFRACTORY PARTIAL SEIZURES: A POST-HOC ANALYSIS

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Rationale: Depression and anxiety are common psychiatric comorbidities in patients with epilepsy. The objective of this analysis was to explore the relationship between anxiety and depression symptoms and baseline seizure rate and response to adjunctive pregabalin therapy using data from 2 clinical studies of flexible-dose pregabalin as adjunctive treatment for partial-onset epilepsy.

Methods: Study 1079, a randomized, placebo-controlled trial, and study 1088, an uncontrolled, open-label trial, evaluated the safety and efficacy of flexible-dose pregabalin used adjunctively in patients with partial seizures. Patients were included in these studies who had a diagnosis of epilepsy with partial seizures and whose seizures were not adequately controlled by 1-3 concurrently administered antiepileptic drugs. Patients were required to have experienced e”2 (study 1088) or e”4 (study 1079) seizures during the baseline phase. Hospital Depression and Anxiety Scale (HADS-D and HADS-A), RRatio, and 50% Responder rates were assessments used in both studies. The 28-day seizure frequency was assessed from patient-reported seizure activity recorded daily in diaries during the screening (study 1079, 6 weeks; study 1088, 8 weeks) and the 12-week treatment periods. The relationships between 28-day baseline seizure rate and HADS-A and HADS-D scores were evaluated by Pearson correlation analysis. The relationships between severity of anxiety and depression symptoms (high: HADS score >9; low: HADS score d”9) at baseline and response to pregabalin assessed using RRatio and 50% Responder rates were evaluated descriptively.

Results: A total of 178 patients were enrolled in study 1079 (pregabalin, n=119; placebo n=59; 48.3% male; 100% Asian) and 98 patients in study 1088 (50% male; 100% white). The mean (standard deviation [SD]) baseline 28-day seizure frequency was 5.8 (6.7) in study 1088 and 13.2 (14.5), and 13.2 (19.2) for the pregabalin and placebo groups in study 1079, respectively. The mean (SD) HADS-A/HADS-D scores at baseline were 7.4 (5.3)/5.3 (3.6) for study 1088 and 8.3 (3.9)/9.3 (3.6) and 8.4 (3.7)/9.0 (3.8) for the pregabalin and placebo groups in study 1079, respectively. No correlation was observed between baseline HADS-A or HADS-D scores and 28-day seizure rate at baseline in either study (Pe”0.1). In both studies, improvements with pregabalin in both 50% responder rates and RRatios were observed in patients with either less severe (HADS score d”9) or more severe (HADS score >9) baseline mood symptoms (Table 1).

Conclusions: In this post hoc analysis, no relationship between baseline seizure frequency and anxiety and depression symptoms was found in 2 studies of flexible-dose pregabalin used adjunctively in patients with partial-onset seizures. Furthermore, improvements in seizure reduction measures with pregabalin were observed regardless of the severity of baseline depression and anxiety symptoms. Funded by Pfizer.

Table 1. Assessment of HADS Score on 50% Responder Rate and RRatio

IMAGE: tables/902090_T1.jpg

1.276

VIGABATRIN IN EPILEPSY CAUSED BY TUBEROUS SCLEROSIS COMPLEX: COMPARISON OF INFANTILE SPASMS AND PARTIAL EPILEPSY

Tae-Sung Ko, M. Yum, E. Lee and M. Jeong (Asan Medical Center, Seoul, Republic of Korea)

Rationale: Tuberous sclerosis complex (TSC) is a genetic disorder that characterized by hamartomatous growth throughout the body causing high rates of epilepsy, and mental retardation. Vigabatrin (VGB) is a structural analogue of ã-aminobutyric acid (GABA) that irreversibly inhibits GABA-transaminase under assessment for treatment of infantile spasm and refractory complex partial seizure. The objective of this study is to assess the efficacy of VGB specifically for partial epilepsy and infant spasms caused by TSC.

Methods: Thirty-nine children (M:23, F:16) were included in this study, all of whom had been diagnosed with TSC and epilepsy between 1991 and 2010. Data were retrospectively reviewed for seizure types and the usage of AEDs. In order to avoid the selection bias and to exclude the impact of drug interaction, we reviewed the patients treated with VGB as the first monotherapy or second add-on therapy. The efficacy for VGB was defined as seizure freedom for 8 weeks after initiation for partial seizures and 4 weeks for infantile spasms.

Results: Eleven from 17 patients with partial epilepsy and 20 from 22 patients with infantile spasms used the VGB. For the initial monotherapy, 2 of 6 (33%) patients with partial epilepsy became seizure free and 12 of 15 (80%) patients with infantile spasms became seizure free. Overall seizure free rate of VGB was 45% (5/11) of patients with partial epilepsy caused by TSC and 80% (16/20) of patients with infantile spasms caused by TSC, which was significantly higher than that in patients with partial epilepsy ($p<0.05$). Of the 16 infantile spasms patients with seizure freedom achieved by VGB, 12 patients experienced recurrence of seizure later, and became refractory to medical treatments. Only four patients remained seizure-free, three of them switched from VGB to zonisamide because of risk of long term side effect of VGB.

Conclusions: VGB showed a high efficacy in eliminating infantile spasms with patients with TSC, but not in those with partial epilepsy. Considering the efficacy and the long-term side effect of visual field defect, VGB can be used as first choice for the infantile spasms not for the partial epilepsy in patients with TSC.

1.277

THE EFFICACY OF RETIGABINE 600-1200 MG/DAY IS NOT AFFECTED BY NUMBER OF BACKGROUND AEDS AT BASELINE IN ADULTS WITH DRUG-RESISTANT EPILEPSY

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Rationale: Retigabine (referred to as ezogabine in North America) is a first-in-class antiepileptic drug (AED) that reduces neuronal excitability by enhancing the activity of KCNQ (Kv7) potassium channels. The efficacy of retigabine 600-1200 mg/day was assessed by number of background AEDs at baseline in a pooled analysis of 3 randomized studies.

Methods: Study 205 (Phase IIb), and RESTORE 1 and 2 (Studies 301 [NCT00232596] and 302 [NCT00235755], Phase III) were multicenter, randomized, double-blind, placebo-controlled, parallel-group trials in adults with drug-resistant epilepsy, e”4 partial-onset seizures per 28 days, receiving 1-2 (Study 205) or 1-3 (RESTORE 1 and 2) AEDs, with or without vagus nerve stimulator. Patients were randomized to retigabine or placebo (administered tid) and underwent forced-titration to retigabine 600 or 900 mg/day (Study 205, RESTORE 2) or 1200 mg/day (Study 205, RESTORE 1) followed by an 8- (Study 205) or 12-week (RESTORE 1 and 2) maintenance phase. Change in 28-day total partial-seizure frequency from baseline to double-blind period (titration+maintenance) utilizing rank transformational ANCOVA, and responder rate (e”50% reduction in seizure frequency per 28 days) utilizing logistic regression from baseline to maintenance phase, were assessed in the pooled population and analyzed by number of

background AEDs at baseline. As the integrated analysis determined that some patients received 4 AEDs, efficacy endpoints were analyzed by 1, 2 or e”3 AEDs at baseline.

Results: Retigabine 600 (n=281) and 900 mg/day (n=273) were compared with placebo (n=275) in patients from Study 205 and RESTORE 2; 1200 mg/day (n=259) was compared with placebo (n=248) from Study 205 and RESTORE 1. Overall for both endpoints, results showed no significant interaction between treatment and baseline number of background AEDs. The majority of patients (55.1%) were receiving 2 background AEDs at baseline, with similar proportions of patients receiving 1 or e”3 AEDs (23.5% and 21.5%, respectively). Statistically significant differences were observed in the change from baseline in 28-day total partial-seizure frequency with retigabine 900 and 1200 mg/day vs placebo for patients receiving 1, 2 or e”3 AEDs at baseline, and with 600 mg/day for patients receiving 2 AEDs (Table 1). Statistically significant differences in responder rate were seen in patients receiving 1, 2, or e”3 AEDs with retigabine 1200 mg/day vs placebo, 900 mg/day vs placebo in patients receiving 2 or e”3 AEDs, and 600 mg/day vs placebo in patients receiving 2 AEDs (Table 2). For both endpoints, there was some evidence of variability in the magnitude of response to treatment by number of background AEDs at baseline and retigabine dosage.

Conclusions: In this analysis, retigabine 600-1200 mg/day demonstrated efficacy in adults with drug-resistant partial-onset seizures receiving 1-3 background AEDs at baseline. Overall, the response to treatment with retigabine was not affected by the number of background AEDs used.

Funded by Valeant Pharmaceuticals International and GlaxoSmithKline.

Table 1. Median Change from Baseline in 28-Day Total Partial-Seizure Frequency by Number of Background AEDs (Double-Blind Period)

IMAGE: tables/889554_T1.jpg

Table 2. Responder Rate by Number of Background AEDs (Maintenance Phase)

IMAGE: tables/889554_T2.jpg

1.278

PHARMACOKINETICS, SAFETY AND TOLERABILITY OF LEVETIRACETAM EXTENDED-RELEASE IN CHILDREN AND ADULTS WITH EPILEPSY

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Rationale: Levetiracetam extended-release tablets (LEV XR; Keppra XR®) qd are indicated by the FDA for adjunctive treatment of partial onset seizures in patients e”16 years old with epilepsy. Pharmacokinetic studies in healthy subjects e”18 years old have shown LEV XR (1000 mg qd) to be bioequivalent to LEV immediate release tablets (LEV IR; 500 mg bid).[1]

This study evaluated the pharmacokinetics, safety and tolerability of LEV XR (1000-3000 mg/day) as adjunctive therapy in children (12-16 y) and adults (18-55 y) with epilepsy.

Methods: This multicenter, open-label, two-arm study enrolled patients with localization-related or generalized epilepsy on 1-3 AEDs. Patients on stable dose of LEV IR had a mg-to-mg conversion into total daily dose of LEV XR (Keppra XR® tablets, 500 mg and 750 mg) administered each morning over 4 to 7 days. For patients not taking LEV IR, LEV XR was administered as 1000 mg/day qd. LEV plasma concentrations were determined at pre-dose, 1, 2.5, 4, 6, and 10h after LEV XR administration on last dosing day using a validated HPLC/MSMS method. Pre-dose concentration was used as 24h concentration. Steady-state C_{max} and AUC_{24h} were obtained by non-compartmental methods, adjusted to a dose of 1000 mg/day ($C_{max,D}$ and $AUC_{24h,D}$ and normalized per kg bodyweight ($C_{max,DW}$ and $AUC_{24h,DW}$). Children and adult values were compared statistically and 90% confidence intervals (CI) on geometric mean ratio were derived. Tolerability and safety assessments included treatment-emergent adverse events (TEAEs), laboratory tests, ECGs, vital signs, physical and neurological examinations, and concomitant AED concentrations.

Results: Twelve children (6M/6F; mean [range] age 14.9 y [13-16]) and 13 adults (5M/8F; 41.8 y [24-52]) were enrolled. Nine children and all adults were diagnosed with localization-related epilepsy. Children were most frequently on one concomitant AED. Three children and 11 adults converted their LEV IR treatment to LEV XR, the others initiated LEV XR. In both children and adults, median time to peak LEV XR plasma concentration was 6h (Figure 1). Mean $C_{max,D}$ were 17.3 and 14.9 ìg/mL for children and adults. Corresponding mean $AUC_{24h,D}$ were 265 and 236 ìg*h/mL. Variability on mean AUC_{24h} and C_{max} were similar between children and adults (Table 1). Ratios of $AUC_{24h,DW}$ and $C_{max,DW}$ between children and adults were close to 1 and their 90% CIs were within the 0.80-1.25 limits ($AUC_{24h,DW}$ ratio:0.99; 90% CI:0.81-1.21). In both groups, 25% of the patients reported TEAEs, the most frequent were somnolence, nausea and vomiting (each in 2 [8%] patients). Drug-related TEAEs were reported by 16% of patients. Except one, severe vomiting, all drug-related TEAEs were mild; all TEAEs but one (pruritus) resolved at the end of trial. Tolerability was good for both patients converted from LEV IR to LEV XR and those initiated LEV XR.

Conclusions: In children (13-16 years) and adults with epilepsy, LEV XR qd showed comparable steady-state pharmacokinetics and was well tolerated.

UCB-sponsored (NCT00961441)

1.Rouits *et al.*, Epi. Res. 2009;84:224-231

Table 1: LEV XR Pharmacokinetic Parameters (normalized by dose and body weight)

IMAGE: tables/906502_T1.jpg

SE = standard error of the mean (%)

IMAGE: images/906502_A.jpg

1.279

RESULTS OF A DOUBLE BLIND, PLACEBO-CONTROLLED STUDY OF LEV FOR THE EMERGENCY TREATMENT OF SEIZURES IN CANINE CLINICAL PATIENTS

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Rationale: There are a small number of marketed intravenous antiepileptic drugs, of which only a few have been studied for status epilepticus (SE). Performing human studies in the current regulatory environment is almost impossible without some evidence that the new agent may be effective. Epilepsy and SE occur naturally in dogs with prevalence, presentation, and percentage of refractory cases similar to human epilepsy.

Methods: Informed consent was obtained from the owners of dogs with SE or acute repetitive seizures. Dogs who failed initial benzodiazepine (BZD) treatment were randomized to an IV infusion of 30 mg/kg (n=5) or 60mg/kg (n=4) of the human formulation of levetiracetam (LEV) or to saline placebo. If seizures continued for more than 5 minutes, additional IV BZD or IV phenobarbital was administered per the standard of care for veterinary patients. Dogs were observed for 24 hours in a veterinary ICU and LEV plasma levels were measured.

Results: Nineteen dogs were randomized (9 to LEV and 10 to placebo). In the LEV group 55.6% had no more seizures compared to 10.0% in the placebo group (p=0.0573). In-hospital mortality was 2/9 in the LEV group vs. 4/10 in the placebo group. There were no statistically significant differences in adverse events between the groups.

Conclusions: This proof of concept study provides the first evidence that LEV is safe and effective in canine SE/acute repetitive seizures. Further, naturally occurring canine SE may provide a proof of principle platform for translating drug studies in rodent models to human SE trials.

1.280

A PHASE II STUDY EVALUATING THE SAFETY, TOLERABILITY AND EFFICACY OF PERAMPANEL, A SELECTIVE AMPA RECEPTOR ANTAGONIST, IN PATIENTS WITH REFRACTORY PARTIAL SEIZURES

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Rationale: : Perampanel is an orally-active, selective, non-competitive AMPA receptor antagonist with a long half-life, which has shown broad-spectrum anti-seizure effects in various animal models. Following favorable tolerability in Phase I studies, this study evaluated the maximum tolerated dose and safety of perampanel in a randomized, double-blind, placebo-controlled, parallel-group Phase II trial with a secondary endpoint of efficacy.

Methods: In this study, adult patients with refractory partial-onset seizures with/without secondary generalization receiving 1-3 concomitant antiepileptic drugs were randomized in a 3:1 ratio to one of two treatment arms: perampanel (2-12 mg) or placebo. Perampanel (or placebo) was increased by 2 mg every 2 weeks to a maximum of 12 mg (if the current dose was tolerated). This was a four-part study: 4-week baseline, 12-week titration, 4-week maintenance, and a 4-week follow-up. Secondary endpoints included proportion of responders (patients with e”50% reduction in seizure frequency from baseline) and seizure reduction.

Results: Of 48 patients randomized (38 perampanel and 10 placebo), all were analyzed for safety and 47 for efficacy. Six patients (60%) in the placebo arm and 12 patients (32%) in the perampanel arm reached the 12 mg dose level. During the maintenance period, 11 of the 12 patients remained on the 12 mg dose for the entire duration. From a Kaplan-Meier analysis of the safety population, the proportion of patients estimated to tolerate each perampanel dose was: 2 mg (100%; n=38), 4 mg (97%; n=36), 6 mg (86%; n=34), 8 mg (55%; n=28), 10 mg (48%; n=16), 12 mg (44%; n=12). No drug-related serious adverse events occurred and the incidence of treatment-emergent adverse events (TEAEs) was similar between groups (84% perampanel vs 80% placebo). TEAEs considered to be probably/possibly drug-related and occurring more frequently in the perampanel group were dizziness (58% vs 10%), somnolence (32% vs 0%), abnormal coordination (8% vs 0%), diplopia (5% vs 0%), nausea (5% vs 0%), asthenia (5% vs 0%), gait disturbance (5% vs 0%) and insomnia (5% vs 0%). Drug-related nausea, gait disturbance and insomnia were only observed at perampanel doses >6 mg. These TEAEs were all mild to moderate, except severe dizziness (n=3). The study was not powered to detect statistical significance in efficacy endpoints. Compared with the placebo group, patients receiving perampanel tended towards a higher responder rate (40% vs 22%; *P*=0.333) and median percentage seizure reduction (40% vs -2%; *P*=0.130) in the overall treatment phase.

Conclusions: The study demonstrated the tolerability of perampanel doses of 2 mg to 12 mg/day with no safety issues identified in this small study. There was also a preliminary suggestion of efficacy. Based on results from this and other studies, 3 Phase III studies are ongoing to further evaluate the efficacy and safety of perampanel.

(Support: Eisai Inc.)

1.281

CLOBAZAM FOR TREATMENT OF MEDICALLY REFRACTORY SEIZURES

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Rationale: Clobazam is a 1,5 benzodiazepine which has been available and used widely for treatment of seizures and anxiety in many countries other than the United States since the 1970’s. Recently, Phase III clinical trials sponsored by Lundbeck, Inc, studying the safety and efficacy of clobazam in patients with Lennox Gastaut Syndrome have demonstrated efficacy in reduction of drop as well as non-drop seizures. We report our experience with clobazam for treatment of medically refractory epilepsy in a much more diverse population of children and young adults.

Methods: Between 2006 and 2010, 39 patients were prescribed clobazam for treatment of seizures under a CNMC IRB protocol titled “The Use of Drugs Which are Not Available in the United States for the Treatment of Refractory Seizures and Refractory Movement Disorders”. Clobazam was obtained by the parent/caregiver outside the United States, usually from Canada. Data regarding the patients, including dose of clobazam, seizure type, and dose limiting side effects was obtained via a retrospective chart review.

Results: 25 patients were taking clobazam at the most recent office visit. 14 had discontinued the medication. Demographics and dosing of clobazam is summarized in the table . Only one patient has complete seizure control on clobazam monotherapy. Reason for discontinuation was hypotonia (1), irritability (1), encephalopathy (1), lack of efficacy without other unacceptable side effects (6), increased myoclonic seizures (1), increased pulmonary secretions (2), death not related to clobazam (2). 11 of 18 patients with drop seizures benefited enough that the medication was/is continued. No specific seizure type or

etiology seemed either extremely sensitive to clobazam or refractory to the medication.

Conclusions: Clobazam as adjunctive seizure therapy substantially improved seizure control in over 60% of this extremely medically refractory population of patients. The dose of clobazam which we used is similar to dosing in the Phase III trial. Dose limiting side effects occurred in only 15% and were side effects one would expect with this class of medications. Clobazam may contribute significantly to seizure control in children and young adults with medically refractory epilepsy.

IMAGE: tables/908175_T1.jpg

1.282

LEVETIRACETAM EXTENDED-RELEASE CONVERSION TO MONOTHERAPY FOR THE TREATMENT OF PATIENTS WITH PARTIAL-ONSET SEIZURES: A DOUBLE-BLIND, RANDOMIZED, MULTICENTER, HISTORICAL CONTROL STUDY

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Rationale: Levetiracetam extended-release tablets (LEV XR; Keppra® XR) have been shown to be effective as adjunctive therapy for partial-onset seizures (Peltola et al, 2009). The purpose of this study was to evaluate the efficacy, safety and tolerability of LEV XR during conversion to monotherapy treatment of patients with partial-onset seizures compared with a historical control.

Methods: We conducted a double-blind, randomized, multicenter, conversion to monotherapy study using a historical-controlled design (N01280; NCT00419094). Patients (aged 12-75 years) with uncontrolled partial-onset seizures (2-40 partial-onset seizures/4 weeks) on 1-2 AEDs (d"50% minimum recommended dose for 2nd AED) were randomized 3:1 to receive once-daily LEV XR 2000 mg/day or 1000 mg/day. The study comprised: 8-week baseline, 2-week LEV XR up-titration, 6-week previous AED(s) tapering and 10-week LEV XR monotherapy. The primary efficacy variable was cumulative exit rate (patients meeting exit criteria) at Day 112 after the start of tapering previous AED(s). The primary analysis compared the cumulative exit rates for LEV XR 2000 mg/day versus the historical control. Exit criteria included increase in seizure frequency, severity, duration, occurrence of status epilepticus or new generalized seizure (versus 6 months pre-randomization). Secondary variables included cumulative exit rate (all drop-outs) at Day 112 for LEV XR 2000 mg/day and safety/tolerability for LEV XR 2000 mg/day and 1000 mg/day.

Results: Of 228 patients (mean age 34.1 years; 42.1% male) randomized to LEV XR 2000 mg/day (n=171) and LEV XR 1000 mg/day (n=57), 82.5% and 87.7% completed the study, respectively. The cumulative exit rate for patients meeting exit criteria on LEV XR 2000 mg/day (0.375 [95% CI 0.297, 0.453]; n=158) was significantly lower than historical control (0.653). The results were confirmed in the secondary, worst case analysis with cumulative exit rate (all drop-outs/zero censoring) in LEV XR 2000 mg/day: 0.475 (95% CI 0.397, 0.553). 177/228 (77.6%) patients reported e"1 treatment-emergent adverse event (TEAE) which were mostly of mild to moderate intensity. The most frequently reported TEAEs were (2000/1000 mg/day): somnolence (22.2%/21.1%), headache (18.7%/22.8%) and convulsion (14.0%/17.5%). Only 10/228 (4.4%) patients discontinued study drug because of TEAE.

Conclusions: In conversion to monotherapy for partial-onset seizures, significantly fewer patients taking LEV XR 2000 mg/day met the exit criteria compared with historical controls. Both LEV doses were well tolerated.

UCB-sponsored

Reference: Peltola et al, Epilepsia 2009;50(3):406-14

1.283

EFFICACY AND SAFETY OF CLOBAZAM IN THE TREATMENT OF SEIZURES ASSOCIATED WITH LENNOX-GASTAUT SYNDROME: RESULTS OF A PHASE III TRIAL

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Rationale: In a Phase II study, clobazam (CLB), a 1,5-benzodiazepine, decreased the weekly frequency of drop seizures associated with Lennox-Gastaut syndrome (LGS). We conducted a Phase III trial to demonstrate the efficacy and safety of CLB for LGS.

Methods: This prospective, double-blind, placebo-controlled trial compared 3 oral dosages of CLB with placebo as adjunctive therapy for LGS. Patients 2 to 60 years of age with LGS (documented by both clinical and electroencephalographic criteria) enrolled at 66 sites. Following a 4-week baseline phase, patients who had e"2 drop seizures per week were randomized to placebo or 1 of 3 dosages of clobazam (0.25, 0.5, and 1.0 mg/kg/day), up to a maximum daily dosage of 40 mg. Treatment included a 3-week titration phase, followed by a 12-week maintenance phase. The primary endpoint was the percentage decrease in mean weekly frequency of drop seizures during the maintenance vs. baseline phases for the modified intention-to-treat (mITT) population. The mITT analysis included all patients who had entered the maintenance phase. Secondary and exploratory outcomes included response rate thresholds for drop seizures (e.g., e"75%, e"50%, e"25%); mean weekly frequencies of non-drop seizures; and physicians' and caregivers' global assessments. Safety assessments included periodic physical examinations, laboratory evaluations, and adverse event information. Statistical significance was prespecified as pd"0.01 for primary endpoints and pd"0.05 for secondary measures.

Results: 301 patients were screened, 238 were randomized, 217 comprised the mITT population, and 177 completed the study. At baseline, patients' mean age was 12.4 years. 60.5% were male. Demographics and clinical characteristics were similar between groups. There was a statistically significant decrease in mean weekly frequency of drop seizures in all three groups receiving CLB vs. placebo (table). The low dosage, 0.25 mg/kg/day, did not achieve statistical significance by the pd"0.01 criterion.

In addition, CLB resulted in statistically significant dosage-related increases in the numbers of patients experiencing e"75% and e"50% decreases in drop seizures vs. placebo for the high-dosage group (63% vs. 11% and 78% vs. 32%, pd"0.05) and the medium-dosage group (38% vs. 11% and 59% vs. 32%, pd"0.05), respectively. High-dosage CLB decreased the frequency of non-drop seizures vs. placebo (not

statistically significant), and all 3 dosages led to improvements in global assessments by physicians and caregivers vs. placebo (pd”0.05). Somnolence, lethargy, drooling, upper respiratory infections, and behavioral abnormalities were the most frequent treatment-emergent, adverse events reported for CLB in this trial.

Conclusions: In this study, clobazam 0.5 and 1.0 mg/kg/day statistically significantly decreased the weekly frequency of drop seizures associated with LGS. Clobazam was generally safe and well-tolerated.

Percentage Decreases in Average Weekly Rate of Drop Seizures (mITT Population)

IMAGE: tables/904254_T1.jpg

[a]Two-sided, pairwise comparison of each clobazam dosage with placebo (ANCOVA) with treatment, pooled center, and baseline seizure rate as model effects.

1.284

SAFETY OF LACOSAMIDE MONOTHERAPY IN MIGRAINE PROPHYLAXIS, FIBROMYALGIA, AND OSTEOARTHRITIS: PLACEBO-CONTROLLED EVALUATIONS

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Rationale: Lacosamide is a recently-approved antiepileptic drug (AED) for the adjunctive treatment of partial-onset seizures in adults and is available in oral and IV formulations. Based on results of preclinical testing, the efficacy and safety of oral lacosamide monotherapy for nonepilepsy indications of migraine prophylaxis (Trial SP906; NCT00440518), fibromyalgia (Trial SP887; NCT00401830), and osteoarthritis (Trial SP905; NCT00485472) were evaluated in three randomized, placebo-controlled, proof-of-concept trials. Lacosamide doses of 100, 300, and 400 mg/day were evaluated depending on indication. Though efficacy assessments did not show significant differences for the primary variable using the study designs chosen, safety assessments from the individual trials provide a placebo-controlled evaluation of the safety profile of lacosamide AED monotherapy up to 17 weeks.

Methods: After a baseline phase of up to 6 weeks depending on indication, subjects were randomized to placebo or lacosamide in 2 equally divided doses. Subjects were titrated to their target dose in weekly increments of 100 mg/day, then maintained at that dose for 8 weeks (fibromyalgia and osteoarthritis) or 14 weeks (migraine), followed by taper and discontinuation of trial medication. Safety and tolerability were evaluated by adverse event (AE), clinical laboratory, ECG, and vital signs (including body weight) data.

Results: A total of 525 subjects were randomized and received treatment (migraine: n=72 placebo, n=72 lacosamide 100 mg/day, n=74 lacosamide 300 mg/day; fibromyalgia: n=81 placebo; n=78 lacosamide 400 mg/day; osteoarthritis n=76 placebo; n=72 lacosamide 400 mg/day). There was a similar gender distribution across all indications, with a higher percentage of females (85%) enrolled than males. The osteoarthritis trials had the largest number of subjects e”65 years of age (~40% placebo; ~45% lacosamide). More subjects in the lacosamide 400 mg/day groups for fibromyalgia (6.4%) and osteoarthritis (11.0%) withdrew due to an AE than in the respective placebo groups (2.5%) and (6.6%). Fewer subjects in the lacosamide 300 mg/day group for migraine (2.7%) withdrew due to an AE than in the placebo group (6.9%) or the lacosamide 100 mg/day group (9.7%). The most common AE leading to lacosamide discontinuation was vertigo (4.2%) for osteoarthritis, dizziness and headache (3.8% each) for fibromyalgia, and chest pain (2.8 %) for migraine (100 mg/day). The most common AE leading to discontinuation in a placebo group was nausea (2.8%) in the migraine trial. No clinically relevant influence of lacosamide on laboratory values (including cholesterol and triglycerides) or vital signs was observed. Lacosamide was associated with a small increase in mean PR interval. Lacosamide had no effect on heart rate or QRS duration and did not prolong QT/QTc interval.

Conclusions: Safety data from randomized, placebo-controlled trials for migraine prophylaxis, fibromyalgia, and osteoarthritis demonstrated that lacosamide as AED monotherapy for up to 17 weeks was well-tolerated in these predominately female populations.

1.285

PHARMACOKINETICS AND SAFETY OF ORAL AND INTRAVENOUS TOPIRAMATE IN ADULT VOLUNTEERS

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Rationale: Topiramate (TPM) is a widely prescribed antiepileptic drug. An intravenous (IV) formulation of TPM, solubilized in a cyclodextrin matrix (Captisol), is being developed with the long-term goal of evaluating its safety and efficacy in neonatal seizures. Prior to using an investigational IV TPM formulation in children and neonates, the pharmacokinetics (PK) and safety of the formulation must be determined in adults. The immediate aims of this study were to characterized the PK and safety of IV and orally administered TPM, using clinically relevant doses, in healthy volunteers.

Methods: This study utilized a two-way crossover design involving administration single oral and IV TPM doses to 12 adult volunteers. Two subjects received 50 mg of IV TPM over 15 min and 50 mg of oral TPM following a 2 week washout period. The remaining 10 volunteers received 100 mg of IV and oral TPM using the same protocol. Subjects were admitted to Prism Research, a clinical research facility, the day before the studies. Subjects underwent physical and neurological examinations, had EKG recordings and routine laboratory tests. Subjects remained in the facility for 24 hr. for collection of PK blood samples and safety assessments. Additional blood samples were collected and assessments performed at 48, 72, 96, and 120 hr after dosing. Plasma TPM concentrations were measured using a LC-MS method. Concentration-time data was analyzed using a noncompartmental approach with WinNonLin 5.2.

Results: All subjects completed the study. The mean (± SD) bioavailability was 109 ± 10.8%. Half-life, distribution volume, and clearance following IV and oral dosing were 42.3 ± 6.2 and 41.2 ± 7.5 hrs, 1.06 ± 0.26 and 0.94 ± 0.24 L/kg, and 1.33 ± 0.26 and 1.22 ± 0.26 L/hr, respectively. No changes in heart rate, blood pressure, EKG, or infusion site reactions were observed. Mild cognitive adverse events and ataxia occurred between dosing and 2 hr post dose and resolved by 4 hr regardless of route. Many subjects on onset of CNS effects during the 15 min IV infusions.

Conclusions: The results from this study provide new information about TPM disposition. In healthy adults, oral TPM is bioequivalent to IV TPM. The extended half-life following IV and oral dosing

indicates TPM can be given once daily in many patients not taking enzyme inducing medications. Minimal variability in the distribution volume permits use of loading doses to rapidly attain targeted concentration. Mild, but detectable, neurological effects occurred during the infusion demonstrating that TPM quickly enters into the brain. Intravenous infusion of 50 to 100 mg over 15 min appears to be safe. Results from this pilot study will inform the design of subsequent studies in children and newborns, including controlled clinical trials intended to determine the efficacy and safety of IV TPM for neonatal seizures.

This study was supported by a grant from the New Therapy Grant Program, Epilepsy Research Foundation. CyDex Pharmaceuticals provided grant to support preparation of the IV TPM formulation.

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FIRST LONG-TERM EXPERIENCE WITH THE ORPHAN DRUG RUFINAMIDE IN PATIENTS WITH DRAVET SYNDROME

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Rationale: Rufinamide (RUF) is an FDA-approved new anticonvulsant licensed as an orphan drug for patients with Lennox-Gastaut-Syndrome (LGS) in Europe.

In this retrospective European multicenter study we evaluated the efficacy of RUF in patients with Dravet syndrome (DS) and refractory seizures.

Methods: 20 patients (17 male, age 3-23 years, mean 12.2 years) in whom RUF was started before February 2010 were included. All of them showed mental retardation (7 mild, 9 moderate, 4 severe).We analyzed the responder rate (defined as a 50% seizure reduction), tolerability and retention rate after 6 and 12 months.

In 16 patients an SCN1A mutation was detected. Before the RUF trial patients had been treated with 2-15 (mean: 7) antiepileptic drugs. The most frequent antiepileptic co-medication at the beginning of RUF was valproic acid (10 patients).

Results: The responder rate after 6 months was 20% (4 of 20). In all of them seizure reduction was observed within the first 3 months of treatment. The responder rate after 12 months was 5% (1 of 20).

The retention rate was 35% (7 /20) after 6 months and 25% (5/20) after 12 months.

RUF treatment was stopped due to aggravation of seizures in 6 patients, no effect (45%; 9 of 20) or side effects (10%; 2 of 20). Side effects were fatigue, gait disorders, decreased appetite, nausea, vomiting, abdominal pain and aggressive behaviour.

The duration of treatment was between 9 days and 30 months (mean 9.2 months), only 2 patients still continue, since 29 and 32 months. One of the responders had to stop the medication with RUF due to side effects.

The mean dose of the patients treated with RUF longer than 3 months was 32.9 mg/kg/d (range from 9.5 mg/kg/d to 72 mg/kg/d).

Conclusions: The efficacy and long-term retention rate in our patients with DS and refractory seizures is far less than in our patients with LGS and Doose syndrome. One third of our patients experienced a seizure aggravation. RUF does not seem to be a suitable option for the long-term treatment in patients with DS.

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THE INCIDENCE OF COGNITIVE ADVERSE EVENTS RELATED TO ESLICARBAZEPINE ACETATE: AN INTEGRATED ANALYSIS OF THREE DOUBLE-BLIND STUDIES OF ESLICARBAZEPINE ACETATE AS ADJUNCTIVE TREATMENT FOR PARTIAL-ONSET SEIZURES

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Rationale: Cognitive dysfunction is frequently observed in patients with epilepsy and represents an important challenge in the management of patients with this disorder.1 In this respect, the contribution of antiepileptic drugs (AEDs) is of relevance, and studies in healthy volunteers have shown that AEDs produce cognitive effects1,2 Eslicarbazepine acetate (ESL) is a novel AED in development.

Methods: We analyzed Treatment Emergent Adverse Events (TEAEs) related to cognition in three double-blind Phase III studies in subjects with partial-onset seizures. We studied all subjects (N=1049) who received at least 1 dose of study medication (400 mg, 800 mg, or 1200 mg of ESL or placebo) as adjunctive therapy to 1-3 concomitant AEDs. Investigators recorded AEs at each visit from Visit 1 and throughout the study (including at early discontinuation and at the post study visit). A TEAE was defined as an event that occurred on or after the date of first dose, or the date of randomization if the dates of the first dose or the onset of the event were missing or incomplete. Cognitive TEAEs were defined as those affecting attention, memory impairment, amnesia, aphasia, bradyphrenia, or psychomotor retardation.

Results: The incidence of cognitive TEAEs in the integrated analysis of three trials is presented by dose group in Table 1. The incidence of cognitive TEAEs was low in all ESL dose groups, with the highest incidence occurring in the ESL 1200 mg group.

Conclusions: Conclusions: Treatment with eslicarbazepine acetate as adjunct therapy to 1 to 3 concomitant AEDs produced a low occurrence of cognitive TEAEs.

Reference:

1. Mula M, et al. Antiepileptic drug-induced cognitive adverse effects. CNS Drugs. 2009;23:121-137.

2. Meador KJ. Cognitive and memory effects of the new antiepileptic drugs. Epilepsy Research. 2006;68:63-67.

Incidence of Treatment Emergent Adverse Events for the Integrated Phase III Epilepsy Studies (Safety Population)

IMAGE: tables/904671_T1.jpg

Abbreviations: ESL=eslicarbazepine acetate; QD=once daily.

[a]Reported AE terms were coded using the MedDRA version 7.0 dictionary for Study 2093-301 and version 9.0 for Studies 2093-302 and 2093-303.

Note: The titration, maintenance, and tapering-off periods were combined. Study 2093-302 did not have a tapering-off period. Study 2093-303 did not have a study arm with ESL 400 mg.

Treatment emergent adverse events are those that occurred on or after the date of first dose or the date of randomization if the date of the first dose was missing.

Adverse events with missing or incomplete onset dates were considered to be treatment emergent unless it could be determined that the event began before the treatment period.

Subjects were counted at most once within each system organ class and preferred term.

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AN OPEN-LABEL EXTENSION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF GANAXOLONE AS ADD-ON THERAPY IN ADULTS WITH UNCONTROLLED PARTIAL ONSET SEIZURES

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Rationale: Ganaxolone (GNX) is a synthetic analog of the endogenous GABA modulator allopregnanolone. GNX 1500mg/day has been shown as safe and effective for the treatment of epilepsy in a 10 wk, double-blind (DB), placebo (PBO)-controlled study of adjunctive therapy in adult outpatients with uncontrolled partial onset seizures (POS) (Tsai,J., Antiepileptic Drug Trials X, Coral Gables, FL, April 2009). A 2 year, open-label extension (OLE) to the DB study was conducted to assess the long-term safety, tolerability and efficacy of GNX.

Methods: Adults (N=124) aged 18 to 69 yrs having POS with or without secondary generalization were enrolled in the OLE at 24 US sites. Subjects received GNX 1500mg/day as 500mg tid or maximally tolerated dose regardless of prior treatment in the DB study. Up to 3 concomitant AEDs at stable doses were permitted.

Results: Of 131 completers in the DB study, 124 (95%) entered the OLE and were dosed for a mean of 262 days. Preliminary analysis shows GNX to be safe and well-tolerated for extended use. The most frequent (>10%) adverse events (AEs) in the OLE were fatigue, headache, dizziness, convulsion, fall, contusion, somnolence, and nasal congestion; most were mild or moderate in severity. SAEs were reported in 17 subjects; 7 were related to the disease being studied. There were no trends of changes in chemistry, vital signs or ECGs that would limit clinical use. No mean changes in weight were observed up to 12 mo; 4 subjects (3%) reported weight increase as an AE. Preliminary analysis of OLE data shows subjects experienced a reduction in mean weekly seizure frequency from baseline to endpoint of 11.8%. The reduction in mean weekly seizure frequency measured at Wk 52 (observed cases) was 32.0%. Mean weekly seizure frequency decreased by 13.6% after 10 wks of open-label treatment for the group that received PBO in the DB study and began GNX in the OLE. This result is similar to the 17.6% decrease seen with GNX treatment in the DB study. DB GNX subjects who continued on GNX in the OLE maintained their response. The overall responder rate (defined as 50% improvement over DB baseline) in the OLE was 21.1%; the rate for observed cases at 52 wks was 42.9%.

Conclusions: Preliminary analysis of data from a 2 year OLE of GNX for adjunctive treatment of refractory POS shows GNX maintained seizure control with extended use and was safe and generally well tolerated.

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AN EXPLORATORY SUBGROUP ANALYSIS OF THE SAFETY AND EFFICACY OF ESLICARBAZEPINE ACETATE ADMINISTERED ONCE DAILY AS CONCOMITANT TREATMENT TO LEVETIRACETAM: AN INTEGRATED ANALYSIS OF TWO PHASE III STUDIES

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Rationale: Eslicarbazepine acetate (ESL) is a novel voltage-gated sodium channel blocker. In two double-blind, adjunct Phase III studies of ESL in subjects with partial-onset seizures, levetiracetam (LEV) was identified as one of the most commonly used concomitant antiepileptic drugs in the study population. To gain an understanding of the efficacy, as well as the nature and risk of Treatment-Emergent Adverse Events (TEAEs) associated with the use of ESL in combination with LEV, a sub-analysis by baseline LEV use was conducted for the double-blind portion of these studies (2093-301 and 2093-302).

Methods: For the efficacy analysis we studied randomized subjects (N=790) who received at least 1 dose of study medication (400 mg, 800 mg, or 1200 mg of ESL or placebo), and who had at least 1 post-baseline seizure frequency assessment during the double-blind portion of these studies. The primary efficacy variable was standardized seizure frequency per 4 weeks over the maintenance period, defined as the total number of seizures reported in the diary during the maintenance period divided by the duration of the period, standardized to 28 days. It was evaluated using analysis of covariance (ANCOVA) that modeled standardized seizure frequency as a function of baseline seizure frequency and treatment. For the safety analysis we studied all (N=797) subjects who received at least 1 dose of study medication during the double-blind portion of these studies. The Investigator recorded AEs at each visit from Visit 1 and throughout the study (including at early discontinuation and at the post study visit). A TEAE was defined as an event that occurred on or after the date of first dose, or the date of randomization if the date of the first dose was missing or incomplete.

Results: Of the 790 subjects included in the efficacy analysis, 96 (12.1%) used concomitant LEV. The LS mean difference from placebo in standardized seizure frequency in LEV subjects was 2.9 (p=0.13), 3.2 (p=0.08), and 2.7 (p=0.14) for the 400-, 800-, and 1200-mg ESL groups, compared to 0.6 (p=0.68), 2.0 (p=0.0008), and 2.2 (p=0.0002), respectively in 694 subjects without LEV use. In the safety analysis of 797 subjects, 98 (12.3%) had LEV use. The most common TEAEs seen in the sub-groups with and without LEV use are listed in Table 1.

Conclusions: In this exploratory analysis, the change from baseline in seizure frequency was numerically similar between subjects taking eslicarbazepine acetate concomitantly with LEV and subjects not taking LEV. The small number of subjects taking eslicarbazepine acetate concomitantly with LEV limited the power of this sub-group analysis.

Treatment Emergent Adverse Events by Baseline Levetiracetam Use for the Integrated Phase III Studies (Safety Population)

IMAGE: tables/904691_T1.jpg

Abbreviations: ESL, eslicarbazepine acetate; LEV, Levetiracetam TEAE, treatment emergent adverse event.

[a]Reported AE terms were coded using the MedDRA version 7.0 dictionary for Study 2093-301 and version 9.0 for Studies 2093-302.

*common is defined as occurring in g"2% of subjects.

Note: The titration, maintenance, and tapering-off periods were combined. Study 2093-302 did not have a tapering-off period. Treatment emergent adverse events are those that occurred on or after the date of first dose or the date of randomization if the date of the first dose was missing. Adverse events with missing or incomplete onset dates were considered to be treatment emergent unless it could be determined that the event began before the treatment period.

Note: Subjects were counted at most once within each system organ class and preferred term.

Note: Subjects may have been taking additional AEDs beyond LEV.

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EFFICACY OF RETIGABINE AS ADJUNCTIVE THERAPY IN TWO RANDOMIZED TRIALS IN ADULTS WITH DRUG-RESISTANT PARTIAL-ONSET SEIZURES: COMPLETERS POPULATION ANALYSIS

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Rationale: Retigabine (ezogabine in North America) is a first-in-class antiepileptic drug (AED) that reduces neuronal excitability by enhancing the activity of KCNQ (Kv7) potassium channels. In the Retigabine Efficacy and Safety Trials for Partial Onset Epilepsy (RESTORE 1 and 2), retigabine 600, 900, and 1200 mg/day proved effective and was generally tolerated as adjunctive treatment for adult patients with partial-onset seizures. This report presents an analysis of the RESTORE 1 and 2 completers populations.

Methods: RESTORE 1 and 2 (Studies 301 [NCT00232596] and 302 [NCT00235755]) were multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase III trials in adults with refractory epilepsy and e"4 partial-onset seizures per 28 days, receiving 1-3 AEDs, with or without vagus nerve stimulator. Patients were randomized to retigabine or placebo (administered tid) and underwent forced-titration to 600 or 900 mg/day (RESTORE 2) or 1200 mg/day (RESTORE 1) followed by a 12-week maintenance phase. One dose reduction to 1050 mg/day was allowed at the first maintenance phase visit in RESTORE 1. The changes in 28-day total partial-seizure frequency and responder rate (e"50% reduction in baseline seizure frequency) from baseline were assessed and analyzed for the completers population, which included patients who completed the 12 week maintenance phase.

Results: In RESTORE 1 and 2, 305 and 538 patients respectively, were randomized to retigabine or placebo and received e"1 dose of study drug (RESTORE 1: 1200 mg/day, n=153; placebo, n=152; RESTORE 2: 600 mg/day, n=181; 900 mg/day, n=178; placebo, n=179). The completers populations for RESTORE 1 and 2 totaled 224 (73%) and 409 (76%), respectively (RESTORE 1: 1200 mg/day, n=97; placebo, n=127; RESTORE 2: 600 mg/day, n=135; 900 mg/day, n=121; placebo, n=153). In the RESTORE 1 completers population, median reduction in seizure frequency from baseline to double-blind period (titration + maintenance) for retigabine 1200 mg/day vs placebo was 53.2% vs 19.0% ($p<0.001$), with responder rates of 53.6% vs 18.9% ($p<0.001$). In the RESTORE 2 completers population, median reduction in seizure frequency from baseline to double-blind period for retigabine 600 and 900 mg/day vs placebo was 33.2% and 44.2%, vs 16.1% (pd"0.001 each), with responder rates of 35.6% and 43.8%, vs 17.0% ($p<0.001$ each). There was no significant difference in the proportion of patients who were seizure free during the double-blind period (RESTORE 1: 1200 mg/day, 1.0%; placebo, 0%; RESTORE 2: 600 mg/day, 0%; 900 mg/day, 2.5%; placebo, 0.7%). Although safety and tolerability were not assessed separately in the completers populations, retigabine was generally tolerated in the overall safety population as presented previously.

Conclusions: In these studies, retigabine 600, 900, and 1200 mg/day were effective compared with placebo in adults with drug-resistant partial-onset seizures in the completers populations, similar to the intent-to-treat populations previously reported.

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SEIZURE-FREE PATIENTS AND SEIZURE-FREE DAYS WITH RETIGABINE 600"1200 MG/DAY COMPARED WITH PLACEBO IN ADULTS WITH DRUG-RESISTANT EPILEPSY

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Rationale: Retigabine (referred to as ezogabine in North America) is a first-in-class antiepileptic drug (AED) that reduces neuronal excitability by enhancing the activity of KCNQ (Kv7) potassium channels. The potential for retigabine to provide freedom from seizures - the ultimate goal of epilepsy treatment - has been evaluated in a pooled analysis of 3 pivotal controlled trials.

Methods: Study 205 (Phase IIb), and RESTORE 1 and 2 (Studies 301 [NCT00232596] and 302 [NCT00235755], Phase III) were multicenter, randomized, double-blind, placebo-controlled, parallel-group trials in adults with drug-resistant epilepsy, e"4 partial-onset seizures per 28 days, receiving 1-2 (Study 205) or 1-3 (RESTORE 1 and 2) AEDs, with or without vagus nerve stimulator. Patients were randomized to retigabine or placebo (administered tid) and underwent forced-titration to retigabine 600 or 900 mg/day (Study 205, RESTORE 2) or 1200 mg/day (Study 205, RESTORE 1) followed by an 8- (Study 205) or 12-week (RESTORE 1 and 2) maintenance phase. The percentage of seizure-free days (defined as a day without any seizures) and the proportion of seizure-free patients were assessed during the maintenance phase and double-blind period (titration and maintenance phases) in an integrated analysis of the 3 pivotal controlled trials.

Results: Patients randomized to retigabine 600 (n=281) and 900 mg/day (n=273) were compared with placebo (n=275) in patients from Study 205 and RESTORE 2; 1200 mg/day (n=259) was compared with placebo (n=248) in patients from Study 205 and RESTORE 1. During both the maintenance phase and double-blind period, there were significant differences in the percentage of seizure-free days at all retigabine dose groups compared with placebo (Table 1). There were no significant differences in the proportion of seizure-free patients receiving retigabine 600 and 900 mg/day compared with placebo during either the maintenance phase or double-blind period, but there was a significant difference for retigabine 1200 mg/day vs placebo for both analysis periods (Table 2).

Conclusions: In this analysis, retigabine 600-1200 mg/day was associated with improvement in the percentage of seizure-free days compared with placebo as adjunctive therapy in adults with partial-onset seizures. Furthermore, a significantly greater proportion of patients were seizure-free with retigabine 1200 mg/day compared with placebo. These results further validate the efficacy of retigabine in patients with refractory epilepsy.

Funded by Valeant Pharmaceuticals International and GlaxoSmithKline.

Table 1. Median Percentage of Seizure-Free Days

IMAGE: tables/889662_T1.jpg

Table 2. Proportion of Patients Who Were Seizure-Free

IMAGE: tables/889662_T2.jpg

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SUCCESSFUL ENROLLMENT IN A PHASE III STUDY EVALUATING THE EFFICACY AND SAFETY OF PERAMPANEL, A SELECTIVE AMPA RECEPTOR ANTAGONIST, AS ADJUNCTIVE THERAPY IN PATIENTS WITH REFRACTORY PARTIAL-ONSET SEIZURES

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Rationale: Perampanel is a selective, non-competitive AMPA receptor antagonist that has demonstrated broad-spectrum anti-seizure effects in various animal models. Two Phase II studies demonstrated tolerability of perampanel doses of 2-12 mg/day when administered adjunctively to patients who were refractory to d”3 AEDs with a maximum of one inducer. Based on this and population PK/PD (pop-PK/PD) analysis, we designed 3 randomized, double-blind, placebo-controlled, parallel-design global Phase III studies with perampanel doses ranging from 2 to 12 mg/day to establish the minimum effective dose and spectrum of efficacious doses. Here we report successful completion of enrollment of the first trial evaluating 3 different doses of perampanel (2, 4 and 8 mg/day) and placebo for treatment of partial-onset seizures (POS) in patients with drug-resistant epilepsy.

Methods: Eligible patients were e”12 years of age with POS, with/without secondarily generalized seizures, treated with 1-3 antiepileptic drugs (AEDs) with a maximum of 1 inducer AED. There was a 6-week pre-randomization baseline phase and a 19-week double-blind (6-week titration, 13-week maintenance) phase. Primary endpoint is the percentage change in 28-day median seizure frequency in the maintenance period relative to pre-randomization. In addition to efficacy and safety, the pop-PK and exposure-response are evaluated with the sparse PK sampling approach for perampanel and concomitant AEDs.

Results: Recruitment was completed in January 2010, with 706 subjects randomized in 24 countries in Europe and Asia-Pacific regions. Among randomized subjects, 49% are female, and the majority (65%) Caucasian, with 16% Chinese and 19% Asian non-Chinese. Median age was 32 years (range 12-72); 91% of patients were between 18 and 65 years; and 8% were <18 years. Most patients received e”2 concomitant AEDs; 15% had 1 AED, 47% 2 AEDs and 38% 3 AEDs. When looking at the use of the 4 older AEDs, 41.3% patients were taking valproic acid, 33.0% carbamazepine, 5.7% phenytoin and 4.1% phenobarbital. The three most commonly used newer AEDs were lamotrigine (35.2%), levetiracetam (33.0%) and topiramate (25.9%).

Conclusions: This is the first Phase III study successfully completing enrollment for a selective AMPA antagonist in patients with POS, with results expected late in 2010.

With the broad patient population enrolled and variety of background AEDs used, the study allows adequate assessment of perampanel as an adjunctive therapy. Testing a broad dosing range, including a likely minimum effective dose and expected therapeutic dose(s), will also provide valuable information needed for appropriate use of the drug.

(Support: Eisai Inc.)

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TOLERABILITY OF RETIGABINE AS ADJUNCTIVE THERAPY IN ADULTS WITH DRUG-RESISTANT PARTIAL-ONSET SEIZURES DURING TITRATION AND MAINTENANCE PHASES

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Rationale: Retigabine (RTG, ezogabine in North America) is a first-in-class antiepileptic drug (AED) that reduces neuronal excitability by enhancing the activity of KCNQ (Kv7) potassium channels. Treatment-emergent adverse events (TEAEs) were assessed from 3 pivotal controlled trials of RTG 600-1200mg/day vs placebo (PBO) in adults with drug-resistant epilepsy and summarized by study phase.

Methods: Study 205 (Phase IIb), and RESTORE 1 and 2 (Studies 301[NCT00232596] and 302[NCT00235755], Phase III) were multicenter, randomized, double-blind, placebo-controlled, parallel-group trials in adults with drug-resistant epilepsy, e”4 partial-onset seizures per 28 days, receiving 1-2 (Study 205) or 1-3 (RESTORE 1/2) AEDs, with/without vagus nerve stimulator. Patients were randomized to RTG or PBO (administered tid) and underwent forced-titration to RTG 600 or 900mg/day (Study 205, RESTORE 2) or 1200mg/day (Study 205, RESTORE 1) followed by an 8- (Study 205) or 12-week (RESTORE 1/2) maintenance phase. TEAEs were summarized by study phase (titration/maintenance), in which only new events were counted for each phase. If an event started during titration and continued into maintenance, it was only counted for titration. If an

event started during titration, resolved, and was reported again during maintenance, it was counted for both phases.

Results: The titration and maintenance populations totaled 1240 and 1041, respectively (titration: PBO, n=427; RTG 600mg/day, n=281; 900mg/day, n=273; 1200mg/day, n=259; maintenance: PBO, n=383; RTG 600mg/day, n=243; 900mg/day, n=226; 1200mg/day, n=189). TEAEs reported in e”5% of patients in any treatment group including PBO tended to be higher during titration vs maintenance. The most frequent TEAEs in both study phases for all RTG doses combined were CNS-related and included dizziness, somnolence, headache and fatigue, but incidences were higher during titration than maintenance for all treatment groups including PBO. During titration, TEAE incidence was dose-related: 58%, 62%, 70% and 82% of the PBO, 600-, 900- and 1200-mg/day groups, respectively. During maintenance, overall incidence of TEAEs was comparable for PBO and RTG 600 and 900mg/day and higher only with 1200mg/day: 58%, 55%, 56% and 72%, respectively. However, an apparent dose relationship was observed for dizziness, confusional state, tremor, abnormal coordination, memory impairment, aphasia, dysarthria and constipation during maintenance. TEAEs that were dose-related in the overall analysis (titration+maintenance) but not during maintenance alone were somnolence, blurred vision, speech disorder, gait disturbance and balance disorder. Urinary tract infection was the only TEAE observed at a greater incidence during maintenance than titration in all RTG doses combined (3% and 2%, respectively).

Conclusions: In this integrated analysis of 3 pivotal controlled trials, RTG 600-1200mg/day was generally tolerated. Fewer new TEAEs associated with RTG occurred during maintenance than forced-titration.

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RETINAL STRUCTURE AND FUNCTION IN ADULT PATIENTS WITH REFRACTORY COMPLEX PARTIAL SEIZURES TREATED WITH SABRIL® (VIGABATRIN): AN OPEN-LABEL, PHASE IV STUDY

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Rationale: Vigabatrin (VGB) was approved in the US in 2009 as adjunctive therapy for adult patients (pts) with refractory complex partial seizures (rCPS) who had inadequately responded to several alternative treatments, and as monotherapy for pts 1 month to 2 years of age with infantile spasms. An important safety issue for VGB is the risk of vision loss, characterized by bilateral concentric constriction of visual fields in e”30% of pts. Robust data assessing incidence of changes early in treatment are lacking. To define incidence and magnitude of changes in retina structure and function, we are designing a prospective, 1-year open-label trial of VGB as adjunctive therapy for adults with rCPS.

Methods: An estimated 80 pts with rCPS e”1 years (with e”2 seizures per month averaged over prior 3 months) will be enrolled at ~25 sites over 18 months. Pts e”18 years of age naïve to VGB will receive open-label VGB therapy at dosages determined by the investigators following guidance in the US product label. Pts must have failed e”3 prior therapies for lack of efficacy and must be receiving concomitant anti-epileptic drugs. Automated kinetic and static perimetry assessments will be conducted at baseline, and 3, 6, 9, and 12 months following initiation of VGB. Retinal structure will be evaluated at the same time points through optical coherence tomography (OCT). Key endpoints will include mean change from baseline in visual field width (kinetic perimetry); change from baseline in mean deviation of visual field (static perimetry); and mean change from baseline in retinal nerve fiber layer thickness (OCT). Secondary evaluations will include visual acuity and color vision, changes in ophthalmologic parameters as functions of time and exposure to VGB, and assessments of physical function, quality of life, and vision-related symptoms. Safety of VGB will be evaluated via ophthalmologic assessments, physical examinations, neurologic examinations, and ongoing adverse event assessment. All pts who receive at least one dose of VGB will be included in all safety analyses.

Results: After commencing VGB therapy, pts will be assessed every 3 months through static and kinetic perimetry, OCT, visual acuity, and color vision tests. This study will not mandate VGB discontinuation based on visual field results. If a deficit is discovered, the investigator will conduct a benefit/risk assessment and discuss with the patient. If VGB is discontinued, one final examination will occur, 3 months after discontinuation. If a >10% decrease in the horizontal extent of visual field of either eye for a given patient (compared with previous examination) is detected, perimetry tests will be repeated within 2 weeks to confirm the change.

Conclusions: This study is designed to address 2 unresolved issues of VGB-induced vision loss — 1) a better definition of onset and progression, and risk of developing vision loss during the first year of VGB exposure, and 2) a robust and more widely available methodology than perimetry for monitoring retinal changes in pts receiving VGB.

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IDIOPATHIC GENERALIZED EPILEPSY AND CHOICE OF ANTIEPILEPTIC DRUGS

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Rationale: To report our experience in the Middle East region of how often patients with Idiopathic generalized epilepsy (IGE) are placed on inappropriate antiepileptic drugs (AEDs) before being seen at an epilepsy referral clinic.

Methods: We retrospectively reviewed the EEG reports of patients at our EEG lab from the year 2004-2009. Patients with a confirmed diagnosis of IGE based on EEG criteria were identified. We reviewed their demographic data, work up for epilepsy, seizure types, and seizure frequency prior to evaluation at an epilepsy clinic. The primary objective of this study was to study the percentage of patients with IGE receiving inappropriate AEDs. The secondary objective was to determine the percentage change in seizure response rate after evaluation at the epilepsy clinic and initiating appropriate AEDs if indicated.

Results: 109 patients were identified, ages 12-56, mean 26, with seizures duration of 1 month to 30 years, mean 10 years. When initially seen, 32.11 % were on broad-spectrum (adequate) AED only, 25.68 % on ill-advised AED only and 15.59 % on various combinations. Of the patients who were receiving ill-advised AED, 28.44 % were seizure-free and 39.44 % were doing poorly. These were converted to broad-spectrum AED; of which, 50% became better controlled. In addition, 24.8% of patients were previously on no AEDs prior to the clinic visit and once placed on adequate AEDs were controlled.

Conclusions: Our findings confirm the previous views that a poor choice of AED is still the main cause of IGEs that are seemingly difficult to control and indicate the importance of establishing specialized epilepsy clinics to evaluate these patients and make the appropriate changes. In our region, the inappropriateness of some AEDs for IGE is either not well known or neglected.

1.296

RISK OF RETINAL TOXICITY OR VISUAL FIELD IMPAIRMENT FOR PEDIATRIC PATIENTS TREATED WITH VIGABATRIN

E. Lynch, H. Greiner, D. Franz and D. Krueger (Cincinnati Children's Hospital Medical Center, Cincinnati, OH)

Rationale: Despite proven efficacy for the treatment of infantile spasms (IS) and partial-onset seizures in adults, vigabatrin use has been limited by concerns of drug-associated retinal toxicity resulting in peripheral vision loss. The purpose of the current study was to assess the incidence of acquired visual field constriction and retinal toxicity for pediatric patients with IS or refractory complex-partial epilepsy treated with vigabatrin.

Methods: We conducted a retrospective chart review of data for patients followed in the child neurology clinics at Cincinnati Children's Hospital between 1998-2010 who were treated with vigabatrin. Data collected included age; seizure etiology, frequency, and description; and vigabatrin dosing regimen. Ophthalmologic specialist evaluation reports were reviewed for methodology of assessment and any abnormalities detected. Only patients under the age of 21 who were evaluated by a pediatric ophthalmologic specialist subsequent to initiating treatment with vigabatrin were included.

Results: Of 146 patients treated with vigabatrin during the analysis period, 53 were able to be included in the present analysis. Patients' ages ranged from 0-12 years (mean age was 3.0 years) when vigabatrin was initiated. Patients were treated an average of 23.9 months, with an average daily dosage at steady state of 88 mg/kg/day. Ophthalmologic assessments were performed, on average, after 19.1 months of therapy (range 0-68 months). Pre-existing, chronic non-refractive vision or fundoscopic abnormalities were noted for 14 of 43 patients with tuberous sclerosis complex (TSC), which manifested most commonly as retinal astrocytic hamartomas. Non-refractive abnormalities (most commonly optic nerve hypoplasia or cortical blindness) were noted at baseline for 6 of 10 patients without TSC. In addition to age- and cognitive-related difficulties, several ophthalmologists cited these findings as reasons limiting detailed functional visual field assessment or formalized testing with electroretinography (ERG). Nonetheless, no evidence of visual field impairment or retinal toxicity was observed for 52 of 53 patients (98%). Vigabatrin-associated toxicity could neither be confirmed nor excluded for 1 patient noted to have decreased scotopic but normal photopic function in both eyes, as determined upon ERG. Moreover, 34 of 53 patients (64%) have continued on current therapy because of favorable seizure control via vigabatrin therapy and the absence of identifiable treatment-related retinal toxicity or peripheral vision loss.

Conclusions: Although concern for retinal changes and visual field constriction is widespread among parents and practitioners alike, actual incidence of vigabatrin-associated toxicity is extremely low in pediatric patients with epilepsy.

1.297

MALADAPTIVE BEHAVIOR IN CHILDREN BORN TO WOMEN WITH EPILEPSY

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Rationale: Literature suggests that children born to women with epilepsy may be at an increased risk of maladaptive behaviour. However, research completed to date has involved small numbers of children or has often been retrospective in nature, increasing the chance of biased reporting.

Methods: As part of the Liverpool and Manchester Neurodevelopment Group's prospective study, data has been collected on the maladaptive behaviour of children born to mothers with epilepsy. This cohort is prospectively recruited prior to birth and monitored until six years of age. The Behavioural Assessment System for Children (BASC-II) was administered to mothers of children assessed at six years of age, by a researcher blinded to the exposure type.

Results: Seventy nine percent (n=272) of questionnaires were returned (48 exposed to carbamazepine, 48 to valproate, 23 to lamotrigine, 24 to polytherapy and 129 control children). No significant differences were found in the externalising difficulties of hyperactivity and aggression but children exposed to polytherapy treatments scored significantly higher for conduct difficulties in comparison to control children ($p=0.012$) and children exposed to valproate ($p=0.023$). No significant differences were found for the internalising difficulties of anxiety, depression or somatisation. Children exposed to valproate showed a trend towards significance for atypicality ($p=0.055$) and reached a significant level of difference for attentional problems ($p=0.005$) in comparison to the control children.

Significantly more children exposed to polytherapy fell within the 'at risk' (>60) or clinical range (>70) for hyperactivity (27%, $p=0.012$), aggression (27%, $p=0.028$), conduct difficulties(27%, $p=0.008$) and attention (33%, $p=0.002$) in comparison to control children. Children exposed to valproate fell more frequently within the 'at risk' or clinical range, and this reached significance for withdrawal (21%, $p=0.019$) and attention (31%, $p<0.001$). There was also an increase in 'at risk' scores for the children exposed to carbamazepine in utero for conduct difficulties (18%, $p=0.33$), depression (18%, $p=0.017$) and attention (21%, $p=0.027$). No increase in maladaptive behaviours was found for children exposed to lamotrigine. Gestational age at birth and intellectual abilities were strongly associated with attentional deficits and higher levels of withdrawal.

Conclusions: Children exposed in utero to polytherapy treatment or monotherapy valproate show a higher incidence of maladaptive behaviour as a group. Increased rates of 'at risk' and clinical levels of maladaptive behaviour were more frequent in all antiepileptic drug groups with the exception of lamotrigine.

1.298

THE TIME TO STOP (TTS) STUDY: ANTIEPILEPTIC DRUG WITHDRAWAL AFTER EPILEPSY SURGERY IN CHILDREN

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Rationale: The aims of the Time to stop (TTS) study are: 1) to evaluate current antiepileptic drug (AED) withdrawal policies after epilepsy surgery in children, 2) to explore determinants of timing of AED discontinuation, and 3) to study the relation between timing of withdrawal and seizure recurrence during/ after AED withdrawal as well as eventual seizure outcome.

Methods: The TTS is an international retrospective consecutive cohort study of 778 children, operated between 2000 and 2008 in 15 medical centers in 8 countries, in whom it was decided to start AED withdrawal after postoperative seizure freedom. First, using uni- and multivariate linear regression analysis, preoperative variables previously described to independently predict postoperative seizure outcome were related to time intervals between surgery and start of AED withdrawal (I_start), and complete discontinuation of AED (I_stop). Second, time intervals of withdrawal were related to seizure recurrence during or after AED withdrawal and to eventual outcome (Engel 1 > 1yr) using a Cox regression analysis. To this model we added previously identified other predictors of seizure outcome.

Results: Mean I_start (n=778) was 16.8 months (SD ± 13.8, range 0-82) and mean I_stop (n=446) was 30.4 months (SD ± 18.0, range 0-105). The interval between start and complete discontinuation of medication (I_withdrawal) was 13.6 months (SD ± 12.8, range 0-68). Time intervals were independently associated with: participating center, number of preoperative AEDs, direct postoperative seizure freedom, etiology, presence of bilateral MRI abnormalities, type of surgery, IQ scores, intracranial recordings performed and presence of epileptic abnormalities on postoperative EEG. During or after AED withdrawal, 96 children had seizure recurrences. Eventually only 26 children were not seizure free. Shorter I_start, bilateral MRI abnormalities, older age at surgery, higher number of AEDs tried preoperatively, and incomplete resection were associated with seizure recurrence during/ after AED withdrawal. If I_stop was added to the model, however, the only independent predictive variables were I_stop, bilateral MRI abnormalities and incomplete resection. Time intervals were not associated with eventual seizure outcome. Predictors for unfavorable eventual seizure outcome were: higher number of preoperative AEDs, left sided surgery and incomplete resection.

Conclusions: Early completion, but not start, of AED withdrawal independently increases the risk of seizure recurrence during or after AED withdrawal. Timing intervals, however, are not related to eventual seizure outcome. Early AED discontinuation may unmasks surgical failure but not at the expense of eventual seizure freedom. These results justify a future multicenter randomized trial to study benefits and safety of very early start of AED withdrawal after epilepsy surgery in children.

1.299

A COMPREHENSIVE REVIEW OF THE LANGUAGE ABILITIES OF CHILDREN EXPOSED TO VALPROATE OR CARBAMAZEPINE IN UTERO

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Rationale: Research has highlighted that the language abilities of young children exposed in utero to valproate or carbamazepine may be compromised. However, the level of impairment and the language systems affected remain unclear and require investigation to allow for a comprehensive understanding.

Methods: Following the administration of neuropsychological assessment at six years of age, conducted by the Liverpool and Manchester Neurodevelopment Group, mothers of children exposed to either valproate or carbamazepine were approached to enrol their child for further, more in depth, assessment of their child's language abilities. Children whose mothers consented were assessed using the Clinical Evaluation of Language Fundamentals (4th Edition). Control children matched for age, gender and non-verbal IQ were recruited for each child with a history of exposure to either valproate or carbamazepine monotherapy throughout gestation.

Results: Thirty children exposed to valproate and 30 children exposed to carbamazepine aged between six and seven years were assessed along with matched control children. The children exposed to valproate in utero in comparison to control children had significantly poorer mean language scores across the domains of core language ($p<0.001$), receptive language ($p<0.001$), expressive language ($p<0.001$), language content ($p<0.001$) and language structure ($p<0.001$). Children exposed to carbamazepine in utero also differed significantly from control children on their overall core language ability ($p=0.042$), their expressive language ($p=0.023$) and in terms of language structure ($p=0.018$).

A significant increase in the rate of below average performance (<84) was found for the group exposed to valproate (44%) in comparison to 11% of matched control children ($p=0.005$). Twenty four percent of children exposed to carbamazepine in utero fell below average in comparison to 7% of their matched sample ($p=0.070$). Rates of speech and language therapy were substantially higher in the valproate exposed group (38%) in comparison to the matched control group (18%) and the children exposed to carbamazepine (23%).

Conclusions: Children exposed to valproate or carbamazepine in utero are at an increased risk of poor language ability. For children exposed to valproate the impairment appears to be global. Further investigation of language abilities within these exposure groups is required in larger cohorts where the effects of dose can be considered.

1.300

VIGABATRIN FOR TREATMENT OF PARTIAL-ONSET CHILDHOOD EPILEPSIES

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Rationale: With its proven efficacy for the treatment of infantile spasms and partial-onset seizures in adults, vigabatrin has continued to gain widespread acceptance despite concerns of potential visual field impairment associated with its use. The purpose of the current study was to assess the effectiveness of seizure control achieved with vigabatrin for pediatric patients with refractory epilepsy after 6 months of therapy.

Methods: We conducted a retrospective chart review of patients followed in the child neurology clinics at Cincinnati Children's Hospital between 1998-2010 who were treated with vigabatrin. Data collected included age; sex; seizure etiology, frequency, and description; and vigabatrin dosing regimen. Seizure frequency was categorized through a 0-4 scale, from seizure-free status greater than 1 month (0) to seizure-free status less than 1 day (4). Only patients under the age of 21 who were verified to have been treated for e"6 months, and whose baseline and follow-up seizure frequencies had been recorded, were included in the analysis.

Results: Of 146 patients treated with vigabatrin during the analysis period, 87 were able to be included in the present analysis. Patients' ages ranged from 0-20 years (mean age was 4.3 years). Tuberous sclerosis complex (TSC) was the most likely underlying etiology for seizures (84%). Most patients had daily seizures (often several per day) at baseline and had been treated with other anticonvulsants previous to vigabatrin. Partial-onset seizure (simple partial, complex partial, complex partial with secondary generalization), either alone (49%) or in combination with infantile spasms (40%), was the most common seizure type being treated. With an average daily dosage of 78 mg/kd/day at 6 months, seizure frequency on the 0-4 scale decreased from 3.8 ± 0.5 at baseline to 2.0 ± 1.7 at 6 months ($p<0.001$). Moreover, 69% of patients demonstrated improvements, and 29% went from experiencing seizures daily to being seizure-free at 6 months. Vigabatrin was effective for both TSC ($p<0.001$) and non-TSC ($p=0.015$) patients with partial-onset seizures. Vigabatrin was also effective for patients greater than the age of 2, when infantile spasms were much less likely to have been encountered in conjunction with simple partial and complex partial seizures ($p<0.001$). As of June 2010, 43 had remained on vigabatrin therapy, 20 were able to discontinue medication after resolution or improvement of seizures, and the remaining 24 discontinued vigabatrin because of lack of sustained efficacy, adverse events, parental concerns, or other reasons. None discontinued because of documented ophthalmologic impairment or evidence of retinal toxicity.

Conclusions: Vigabatrin appears to be safe and effective for the treatment of partial-onset epilepsy for pediatric patients with or without tuberous sclerosis complex.

1.301

DIFFERENTIAL DOSING OF ANTIEPILEPTIC MEDICATIONS: HIGHER DOSAGE IN THE EVENING FOR NOCTURNAL SEIZURES

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Rationale: To assess seizure control in patients with predominantly nocturnal epileptic seizures who were started on higher evening doses of antiepileptic drugs (AEDs).

Methods: Patients with focal epilepsy from a tertiary care center with nocturnal or early morning seizures who had received a proportionally higher evening dose of AEDs were included in a retrospective review to assess efficacy and side effect profile of this dosing schedule as compared to median baseline seizure frequency over 12 months (Interquartile range (IQR) 6-30). Patients who had a e"50% reduction in seizure frequency (per month) were considered responders.

Results: Seventeen subjects (9 males; median age 11.9 years (IQR) 8.8-14.6) had seizure onset at a median age of 7 years (IQR 2.5-8.1). Ten presented with a history of developmental delay. Etiologies included malformations of cortical development (n=3), tuberous sclerosis complex (n=1), anoxic encephalopathy (n=3); and was unknown in 10. Clinical presentation in 5 out of these 10 was consistent with a syndromic diagnosis of nocturnal frontal lobe epilepsy (NFLE) and in 3/10 with benign epilepsy with centrotemporal spikes (BECTS). The median number of previous AEDs was 2 (IQR 1-3) and the median number of current AEDs was 1 (IQR 1-2). The median initial seizure frequency per month was 12 (IQR 2.5-45) with a median duration of epilepsy of 6.3 years (IQR 2.6-9.4). After adjusting the nocturnal dose to be higher (median 66.6% of daily dose, range 39-100%) than the morning and/or afternoon ones, median seizure frequency per month was 0 (IQR 0-3) ($p=0.001$). Mean reduction of seizure frequency was 78.5% (SD 38.2%; median 100%, IQR 79.2-100%) and median time of follow-up after the modification was 3 months (IQR 2-7). Fifteen patients were classified as responders, 11 of these became seizure free (5 NFLE, 1 BECTS, 5 with structural lesions), and 4 (2 BECTS, 2 with lesions) with 75-90% of seizure reduction. Two were classified as non responders (both with unknown cause, including one who had failed epilepsy-surgery). Nine subjects (53%) received monotherapy after dose modification with OXC (4), LEV (4), or VPA (1) and in the remaining cases other AEDs (LTG, GBP, PHT, RUF, TGB, TPM) were combined in polytherapy with differential dosing; BID administration was used in 16 out of 17. None of the patients presented worsening of the seizures after dose modification. Two complained of transient side effects: fatigue (n=1) and somnolence (n=1). No meaningful interpretation could be obtained from trough drug levels in our small cohort with differential dosing. However, we feel that trough levels should be performed in the morning and evening to assess whether morning troughs would be higher as expected than evening which would be lower, because of the higher dose in the evening.

Conclusions: Proportionally higher evening dose of AEDs in subjects with nocturnal seizures led to seizure freedom in 64.7%, and in 88.2% to e"50% seizure frequency reduction. Prospective studies need to be done in a larger cohort to validate our observation.

Support: CAPES (Brazil).

1.302

CASE SERIES OF PATIENTS IN REFRACTORY STATUS EPILEPTICUS TREATED WITH INTRAVENOUS LACOSAMIDE

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Rationale: Status epilepticus (SE) is an underdiagnosed life-threatening medical emergency, but limited data is available to guide management. Lorazepam is the accepted first line therapy, with most prior studies supporting Fosphenytoin as second line. Although multiple other anti-epileptic (AEDs) are available, only 2-7% of SE will be stopped with a third line agent or beyond. Lacosamide (LCS) is an AED with a novel mechanism of action and approved as adjunctive therapy for partial seizures in adults. LCS has shown efficacy in mouse models of SE and an intravenous (IV) formulation is available but not FDA approved for SE. Only a single case report has reported the use of IV LCS in stopping nonconvulsive SE. This case series investigates safety profile and potential efficacy of IV LCS in patients with refractory SE on video electroencephalography (EEG).

Methods: Charts were retrospectively reviewed per IRB-approved protocol for patients with continuous EEG-confirmed SE and were treated with LCS during SE. Primary outcomes were cessation of electrographic seizures after administration of IV LCS, as well as safety profile measures. Statistical analysis was performed on SPSS 10.0.

Results: Twenty-seven patients had SE and were treated with LCS, of which 88.9% had nonconvulsive SE. No prior seizure history was found in 59.3%. Only two patients had prior SE. Main etiologies of SE was acute hemorrhage (6), stroke (5), and medically refractory epilepsy (5).

Cessation of SE after LCS occurred in nine patients (33.3%) within 4 hours and 21 patients (77.8%) within 24 hours. LCS was given a mean of 20.8 hours after SE onset for those who had SE cessation within 4 hours and 22.2 hours in the overall group (p=0.308). Mean number of IV AEDs given prior to LCS was 3.3 (range 1-5). Nineteen patients (70.3%) were given an IV AED with sodium-channel mechanism. Mean SE cessation time from end of LCS infusion was 0.78 hours in those who responded within 4 hours and 8.37 hours in those who responded within 24 hours. Patients with no prior history of seizures had a higher responder rate to LCS (p=0.001). SE etiology was not a useful predictor for response.

Serial blood pressures (BP) were obtained in 25 patients. Only two patients had a decrease in BP without significant hypotension. Serial EKGs showed an increase in PR interval in 11 of 16 patients with a mean increase of 24.5 ms in those patients, a mode of 16 ms, and a range of 4-80 ms. One patient had an increase in PR interval >200 ms without clinical symptoms. Serial liver function tests were obtained in 28 patients. Seven patients had an asymptomatic increase in AST and/or ALT. Serial serum creatinine showed a nonsignificant increase in 2 of 26 patients. SE was resolved in 21 patients, while the 6 others expired.

Conclusions: IV LCS is a promising new adjunct agent for the treatment of refractory SE with a favorable safety profile in critically ill population. Prospective studies would better determine the efficacy and potential role of IV LCS in the treatment of SE.

1.303

TREATMENT OF INFANTILE SPASMS WITH VIGABATRIN IN AN ACADEMIC MEDICAL CENTER

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Rationale: Vigabatrin (VGB) is a selective, irreversible inhibitor of GABA transaminase that has been available as treatment for infantile spasms (IS) outside the US for decades. Due to the adverse effect of irreversible peripheral visual field defect, the FDA was reluctant to grant VGB approval in the US. FDA approval was given to VGB in August 2009 as monotherapy for children aged 1 month to 2 years with infantile spasms. VGB (Sabril) is now available through a restricted access program with mandatory guidelines for early detection of vision abnormalities.

Methods: A retrospective chart review was performed on patients treated with VGB at Stony Brook University Medical Center. Patients were identified through a keyword search of a computer log of dictations from January 2001 to April 2010, using the keywords, “vigabatrin”, and “Sabril”. Data was obtained on demographics, and etiology/classification of IS as symptomatic, cryptogenic or idiopathic. Variables included length of treatment, dosing, treatment response, adverse effects, and treatment after VGB was discontinued. The outcome measure of efficacy was spasm cessation and/or resolution of seizures with minimal adverse effects.

Results: Ten patients were identified, 4 males, 6 females, ages 1-14 years. One hundred percent had IS (symptomatic 9/10, idiopathic 1/10). Two of the patients had tuberous sclerosis, and two developed Lennox-Gastaut syndrome. Mean dose was 123 mg/kg/day (range 69 - 182 mg/day) divided BID. Ninety-percent of the patients were treated with a medication prior to VGB (ACTH 6/10, topiramate 3/10, zonisamide 3/10, Phenobarbital 2/10, carbamazepine 1/10, felbamate 1/10, levetiracetam 1/10, and valproic acid 1/10), and one was on a ketogenic diet. Prior to treatment, 4 were cortically blind. Fifty-percent showed cessation of spasms with VGB treatment. Only one patient had an adverse effect consisting of a rash. After treatment with VGB, patients were treated with topiramate (3), zonisamide (3), lamotrigine (1), valproic acid (1), and rufinamide (1). At the time of the study, 5 remained on VGB with a mean treatment duration of 18 months. All patients followed the protocol for ophthalmologic surveillance during treatment and none developed any visual field abnormalities.

Conclusions: VGB is a relatively well tolerated and effective medication for IS, in children with or without tuberous sclerosis. There was no evidence of the development of ophthalmic abnormalities in our limited population. Further analysis of clinical experience is warranted regarding the use of VGB in larger clinical study populations.

1.304

SAFETY AND EFFICACY OF THIOPENTAL FOR REFRACTORY STATUS EPILEPTICUS IN CHILDREN

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Rationale: Thiopental is an ultra short-acting barbiturate that can be used to treat refractory status epilepticus (RSE). The published literature on dosing, safety and efficacy for treatment of RSE in children is limited.

Methods: Retrospective single centre review of children treated with thiopental infusion for RSE between 2004-2009. We collected data on the etiology and type of RSE, antiepileptic drugs used, dosage and duration of thiopental infusion, thiopental-related side effects and efficacy at aborting seizures, and outcome at hospital discharge.

Results: We identified 11 children aged 2 months to 17 years who received thiopental infusions for RSE. All patients were admitted to the ICU, intubated and monitored by continuous EEG. Patients had received between 4 and 7 other anti-epileptic drugs prior to thiopental use. The mean thiopental infusion rate required to achieve EEG burst-suppression or seizure cessation was 4.7 mg/kg/hr (range: 2-8 mg/kg/hr). Short-term seizure cessation was achieved in 8/11 patients, with no clear correlation between efficacy and dosing. The mean duration of thiopental treatment was 69 hrs (range: 40-120 hrs). The mean cumulative thiopental dose was 291 mg/kg (range: 91-526 mg/kg). No life-threatening side effects occurred during treatment, however 10/11 patients required inotropic support and 6/11 developed pneumonia during or shortly following thiopental therapy. Outcome at hospital discharge was variable, ranging from return to baseline function to death following withdrawal of life sustaining therapy.

Conclusions: At the doses above, thiopental infusion achieved short-term seizure cessation in the majority of children, although virtually all children developed hypotension requiring inotropic support, and half developed pneumonia. These findings support the cautious use of thiopental for the treatment of RSE in children.

1.305

CHARACTERISTICS OF USERS OF THE EPILEPSY COMMUNITY OF PATIENTSLIKEME.COM AND COMPARISON WITH A REPRESENTATIVE CLAIMS DATABASE

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Rationale: PatientsLikeMe® (PLM) is a free online platform allowing patients with life-changing conditions to share their disease characteristics and outcomes and learn how to improve their care by peer-peer interactions. The wealth of data collected may also allow research activities for a better understanding of the disease burden, treatment pathways and their impact on patients' lives. The Epilepsy community was launched in the US in January 2010, and a first data export occurred in March. The objective of this analysis is to describe the main characteristics of this preliminary sample and to compare them with Pharmetrics - a claims database representative of the US commercially insured epileptic patient population.

Methods: The PLM epilepsy community allows subjects with epilepsy to record their own characteristics (eg socio-demographics, diagnostic and medical history) and monitor their treatment-related data and outcomes. A survey participation system was built to facilitate longitudinal entry of widely used Patient Reported Outcomes instruments (QOLIE-31, HADS, EQ-5D) alongside treatments, symptoms, and weekly seizure frequency and severity. Pharmetrics has been used to allow comparison with the PLM sample. Patients from the Pharmetrics database who had been diagnosed (clinician reported) with epilepsy and continuously enrolled in Nov-Dec 2008 were selected (N=32 983).

Results: As of March 2010, 1034 users had registered to the PLM Epilepsy community and 761 (73.6%) reported being diagnosed with epilepsy which constitutes the PLM sample selected for this analysis (69.5% females; mean age 36 years; mean duration since diagnosis 17.2 years; Table 1). When comparing PLM with Pharmetrics, mean age appeared similar (mean age: 36 years in both samples), although age distribution differed with a higher proportion of subjects aged 20-50 years for PLM (limited number of children). The proportion of females in the PLM sample was higher (70% in the PLM sample vs 54% in Pharmetrics). The distribution of seizure types showed a slightly larger proportion of patients with Unknown seizure type in the patient-reported PLM source. Treated patients in PLM were more often on polytherapy compared with Pharmetrics. When comparing antiepileptic drug (AED) use, newer AEDs tended to be over-represented in PLM.

Conclusions: Analysis of this preliminary PLM sample shows that compared with Pharmetrics, the PLM Epilepsy community tends to provide an over-representation of i) females; ii) 20-50 years old (reflecting the general characteristics of online users); iii) subjects on polytherapy; and iv) on newer AEDs. These trends illustrate potential self-referral bias. The number of users is expected to increase substantially in the coming months. The representativeness of the PLM Epilepsy population will be re-evaluated as sample size increases. The large number of patients expected and wealth of data collected through this real-life setting will allow further analysis of this epilepsy population segment.

UCB-sponsored

Table 1 PLM and Pharmetrics Population Characteristics

IMAGE: tables/906480_T1.jpg

[1] Lacosamide was not available on the US market during the considered period (Nov-Dec 2008)

1.306

LACOSAMIDE IN CANADA: A PRE-MARKETING, OBSERVATIONAL STUDY

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Rationale: Lacosamide (LCM) is a new anti-seizure drug with a novel mode of action (slow sodium channel blockade), approved in the US, Europe and other countries but not yet in Canada, as adjunct therapy for focal-onset seizures.

Canadian Health authorities allow the use of drugs yet to be approved or not marketed in Canada through a Special Access Program (SAP). This requires a physician's submission to Health Canada and the company responsible for the manufacturing of the drug on a per-patient basis, allowing for accurate monitoring of drug distribution, reporting of side effects and efficacy. Drug companies provide the drug free of cost pending approval.

Clinical trials often do not reflect "real-world" practices. Assessing the performance of LCM as utilized by a group of epileptologists of different backgrounds and dealing with diverse patient populations provides a unique opportunity to evaluate this drug outside the rarefied structure of a clinical trial.

Methods: The drug manufacturer (UCB Canada) was approached to provide the names of practitioners requesting LCM through the SAP. All patients registered in SAP were compiled and their epileptologists contacted to provide details of age, gender, length of therapy, seizure types, response to treatment, side effects (SEs) and type of imaging changes.

Results: Of 57 patients in the SAP, 47 have received LCM for a minimum of 1 month and a maximum of 8. There are 28 females. Age range is 10-63 (median 27.5). Two were on 1 additional AED, 16 on 2, 14 on 3 and 17 on 4 or more. Eight patients have had a surgical procedure and 13 have a VNS device. Forty-two percent had normal MRI. Seizure frequency ranged between 1 - 600 seizures/month (mean: 43). Eight patients had partial complex as the only seizure type.

The average dose of LCM is 300 mg/day (50-600). Eight patients experienced no improvement. Only 2 discontinued treatment due to SEs (one with panic attacks and the other due to nausea, headache and dizziness) and 2 due to inefficacy. Four are up-titrating. Thirteen patients experienced a >50% improvement (2 seizure-free). The remainder had some improvement or are still up-titrating. SEs were reported by 50%, generally transient, mostly dizziness, sedation, nausea and headache.

Conclusions: In this highly refractory group of patients of varying ages and etiologies, LCM provided worthwhile improvement in 25% (2 patients seizure-free). SEs were common but usually transient and well tolerated. Some patients derived benefit in doses as low as 50 mg/day. The observational study is ongoing to collect a larger cohort and follow up over longer period. Aggregate data will be added to this report.

1.307

THE SAFETY AND EFFICACY OF VIGABATRIN FOR PEDIATRIC AND ADULT EPILEPSY IN COMMUNITY-BASED NEUROLOGICAL PRACTICE

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Rationale: Vigabatrin (VGB) was recently FDA approved as monotherapy for pediatric patients with Infantile Spasms (IS) and as adjunctive therapy for adults with refractory complex partial seizures (CPS). Since VGB can cause up to a 30% risk of permanent visual loss, the FDA mandated a Risk Evaluation and Mitigation Strategy (REMS) to screen for Visual Field Deficits (VFDs). Transient MRI signal changes in subcortical areas mirroring intramyelinic edema seen in VGB-treated animals have also been observed, but the necessity of screening is unknown. Clinical data regarding VGB is primarily derived from academic centers with access to sophisticated ophthalmologic practice and neuroimaging. The goal of this study is to determine how its risks are addressed and its efficacy for a broad range of seizure types and epilepsy syndromes in community-based practice.

Methods: Child/adult neurologists identified patients treated in the past 10 years with VGB, and chart review was performed using a standardized form.

Results: The study included 7 children and 3 adults (50% F). Six/ten were treated for IS with the avg. age of seizure onset and VGB initiation of 6.8 mo/13.1 mo. One was treated with ACTH first; only one with VGB monotherapy. Avg. dose was 150 mg/kg/d (125-175 mg/kg/d); median therapy duration was 1 mo (1-108 mo). Etiologies included chromosomal defects-2, lissencephaly, cortical malformation, and cryptogenic-2. The avg. pre-treatment IS frequency/d was 10 (range 1-20); 2 also had CPS and 1 had subclinical seizures. Two were rendered seizure free (33%). One recently started and had an IS reduction from 20 to 1/d; data was not available for 1. One had a significant IS reduction (6-8/d to 1/wk) but with continued 1-2 GTC/wk; another had persistent IS with 0-3/d. Pre-/post-treatment EEG was available in 2 with resolution of all epileptiform activity in both. Post-treatment MRI was not performed. The remaining 4 were treated for LGS, TLE, TS, and unclassified. The median age of seizure onset and median age of VGB initiation was 10 mo/20 yrs. Avg. maintenance was 2.5 g/d with none seizure free or significantly improved. Overall, VFD screening was performed in all but 1 who has cortical blindness: 5 in academic centers, 3 in private, and 1 in an unknown. All had clinical/retinal exams, 4 ERGs, and 2 VFs. No treatment-induced VFDs were observed. Five/seven (71%) were thought to have benefitted and 6/7 (83%) would be treated again (3 missing answers).

Conclusions: Initial results suggest that VGB was both safe and effective in community-based practice. For those treated for IS with known outcomes (n = 5), 40% were rendered seizure free and 80% had a significant reduction. Efficacy was not seen in the older group, possibly due to the relatively low doses used (2/3 of adults were on < 3 g/d). Ophthalmologic assessment was usually performed, with ERG in two-thirds of the children; VGB-related VFDs were not observed yet. MRI was not used to screen for signal changes, so their frequency cannot be stated. Future analysis will examine longer term efficacy and safety.

1.308

CONVERSION FROM ENZYME-INDUCING ANTIEPILEPTIC DRUGS TO TOPIRAMATE OR OTHER NON-INDUCERS: EFFECTS ON C-REACTIVE PROTEIN, HOMOCYSTEINE, AND B-VITAMINS

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Rationale: Our previous investigation demonstrated that conversion from the inducers phenytoin (PHT) or carbamazepine (CBZ) to the non-inducing drugs levetiracetam (LEV) or lamotrigine (LTG) lowers C-reactive protein (CRP). Declines in homocysteine (HCY) occurred only in patients removed from PHT, not those withdrawn from CBZ, however. We sought to determine if similar results would occur when patients are switched to topiramate (TPM) and to acquire additional data to ascertain the effects of individual antiepileptic drugs (AEDs) on CRP, HCY, and B-vitamin levels.

Methods: We converted 13 patients from inducing AEDs to TPM (daily doses of d”150mg except for one patient). CRP, HCY, serum folate, pyridoxal phosphate (B6) and vitamin B12 levels were drawn before and 6 weeks after the switch. These data were then pooled with the previous study (of 34 patients switched to LEV or LTG and 16 normal subjects) to provide greater power to discern the effects of individual drugs. We did additional analyses to determine whether B vitamin deficiency was more common in patients treated with inducing agents.

Results: Conversion from inducers to TPM reduced CRP by 59% ($p<0.001$) and increased folate by 4 ng/ml ($p=0.003$); HCY remained unchanged. Frank B6 deficiency (<5 ng/ml) was observed in 8 of 11 inducer-treated patients (72%); this resolved in 5 of 8 after switch to TPM. When pooled with the previous data, significant declines in CRP occurred after drug switch irrespective of which inducer the patient had been taking (-45%, pd”0.002). Folate rose more prominently in patients withdrawn from PHT (+3.6 ng/ml, $p=0.002$) than in those withdrawn from CBZ (+1.8 ng/ml, $p=0.075$). HCY declined only in the patients taken off PHT (-2.6 umol/L, $p=0.003$), not in patients withdrawn from CBZ (+1.0 ng/ml, $p>0.1$). All of these changes remained significant when compared to those seen in normal subjects. Changes in HCY showed no correlation with change in folate ($p=0.118$). B6 deficiency was seen in 16/33 patients (48%) during treatment with an inducing AED, and in 1/11 normal subjects (9%; Chi-squared, $p=0.031$). After switch to non-inducers, B6 deficiency was present in only 7 patients (21%, McNemar, $p=0.027$). Changes in all measures were similar regardless of whether the patient was switched to TPM, LEV, or LTG.

Conclusions: Conversion from inducing AEDs to TPM or other non-inducing AEDs reduces CRP by about half, strongly implying that cytochrome P450 induction elevates CRP. More work is needed to determine whether there are similar effects on other inflammatory markers. HCY is elevated only in PHT-treated patients, apparently via mechanisms that are not related to induction of folate metabolism. B6 deficiency is endemic in the inducer-treated population; it is possible that this might contribute to the chronic polyneuropathy that has been reported among some patients treated with inducing AEDs. These findings reinforce the notion that enzyme-inducing AEDs cause profuse clinically-relevant metabolic derangements which may be reversible with alterations in therapy.

1.309

RUFINAMIDE EFFICACY IN THE EVERYDAY CLINICAL PRACTISE

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Rationale: Rufinamide (RUF) has demostrated efficacy as adjuntive therapy in adult patients with partial seizures and it has been aproved as adjuntive therapy in patients with Lennox- Gastaut syndrome. Lennox-Gastaut is a catastrophic pediatric epilepsy syndrome characterized by the triad of slow spike and wave pattern on EEG, multiple types of seizures (tonic/atonic, atypical absences and generalized tonic-clonic seizures) and impaired mental development.

Objetive . To present the long term efficacy of RUF in the everyday clinical practise in pediatric and adult patients.

Methods: Multicentric, retrospective study including patients with generalized and focal epilepsies treated with RUF as adjuntive therapy, followed 1 year. Efficacy and safety variables were recorded at 6 month and at 1 year. All seizures were classified according the International League Against Epilepsy Revised Classification of Seizures. Tonic and atonic seizures were considered in the same seizure group.

Results: 39 patients ,26 men-13 women. Mean age 28 (range 7-57), mean age at epilepsy onset 3.7 (range 0-43). 27 (69%) patients were diagnosed of Lennox-Gastaut syndrome or generalized epilepsy with impaired mental development and 8 (21%) patients were diagnosed of focal epilepsies, mainly frontal lobe epilepsies. Connatal anoxia was the most frequent aetiology 10 (25.6%). Mean RUF dose was 1363 mgr (range 400-3200), mean RUF dose/Kg en children 32.7 (range 12.5-66.67 mgr/Kg) , mean RUF dose/Kg in adults 22.2 (range 5-47mgr/Kg) . All patients were treated with RUF on polytherapy, the most frequent associated AED was VPA 20 (51%). 17 patients (44%) discontinued RUF during the 1 year follow up and the main reason for discontinuation was lack of efficacy 10/17 (58.8%). Mean pretreament mensual tonic/atonic seizures 26 , generalized tonic-clonic seizures 3.09 ,atypical absences 49, other (partial) 22. Significative generalized tonic-clonic seizure reduction was observed at 6 months (p:0.013) and at 12 months (p:0.018) in both generalized and partial epilepsies. A tendency in other seizure type reduction was also observed at 6 months (p:0.06). 15 patients referred adverse events 38.46%, being the most frequent nausea , vomiting and weight loss.

Conclusions: RUF was well tolerated in a huge range of dosis showing efficacy in reducing generalized tonic- clonic seizures both in adults and in children with severe epilepsies mainly Lennox-Gastaut Syndrome.

1.310

EFFICACY AND TOLERABILITY OF HIGH ORAL DOSES OF LEVETIRACETAM IN CHILDREN WITH EPILEPSY

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Rationale: Levetiracetam's favorable safety profile, low potential for drug interactions, high bioavailability and linear pharmacokinetics make it an attractive agent for epilepsy in children (Patsalos, P.N., Clinical pharmacokinetics of levetiracetam. Clin.Pharmacokinet. 2004:43,707-724). While typically titrated up to a maximum of 40-60 mg/kg/day, intravenous levetiracetam doses as high as 228 mg/kg/day were effective in controlling acute seizure exacerbations, and were not associated with serious adverse effects in a recent report (Depositario-Cabacar, D.T. et al., High-dose intravenous levetiracetam for acute seizure exacerbation in children with intractable epilepsy. Epilepsia. 2010 Feb 12). We sought to determine whether oral LEV is tolerable and helpful in seizure control at doses higher than 60 mg/kg/day in the pediatric outpatient population.

Methods: A retrospective chart review over a 1.5-year period was performed at the Columbia Comprehensive Epilepsy Center to identify children who were treated with levetiracetam doses titrated above 40-60 mg/kg/day. Data was collected on seizure semiology, epilepsy type, seizure frequency, other antiepileptic drugs used concomitantly with levetiracetam, and adverse effects.

Results: Thirty-two children, ranging in age from 1 year to 19 years, required high dose levetiracetam. Seizure types included epileptic spasms, atypical absence, head drops, myoclonic, astatic, generalized tonic-clonic, and absence seizures. Sixteen children (50%) had complex partial seizures. Five children had generalized and focal seizures. All but one patient were concomitantly treated with other antiepileptic drugs: 13 children (41%) were taking one other antiepileptic drug, 12 (37%) were taking two, 5 (16%) were taking 3, and one child was taking 4. The most common concomitant antiepileptic drugs were valproate and clonazepam. The mean dosage of levetiracetam was 148mg/kg/day (range, 70-275 mg/kg/day), and the mean maximum serum trough level was 47 mcg/ml (range, 20-121 mcg/ml). Levetiracetam serum levels increased linearly with the daily weight-based dosage. A more than 50% reduction in seizure frequency was observed in 14 children (44%), with 5 achieving seizure freedom. No response to high dose levetiracetam was found in 14 children, and worsening of seizure frequency occurred in 4. The proportion of responders was the same in children with generalized and those with partial seizures. A favorable response was recorded in all the main etiologic subgroups. Adverse effects occurred in 4 children (12.5%), and included irritability in 3 children at doses of 73.5, 142, and 150 mg/kg/day, and hyperactivity in a child at a dose of 96 mg/kg/day.

Conclusions: Not only do some children tolerate high doses and serum levels of levetiracetam, but they may also benefit from them, suggesting that doses higher than 60 mg/kg/day may be considered in children who partially respond to the lower doses.

IMAGE: tables/886374_T1.jpg

Table 1. Response by seizure type: GTC (generalized tonic clonic seizures), mixed generalized, mixed focal and generalized, Epileptic spasms (ES).

IMAGE: tables/886374_T2.jpg

Table 2. Response by underlying etiology. MCD = malformation of cortical development; Dravet = severe myoclonic epilepsy of infancy; PVL = periventricular leukomalacia; HIE = hypoxic ischemic encephalopathy; MAE = myoclonic astatic epilepsy.

1.311

EARLY EXPERIENCE WITH LACOSAMIDE: REAL PRACTICE VERSUS TRIAL RESULTS. HOW DO THEY COMPARE?

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Rationale: FDA approval of Lacosamide (LAC) for adjunctive therapy in patients > 17 years occurred in USA mid-2009. A new AED had not been available since 2000 and many patients were candidates for LAC. We reviewed our early experience with LAC as used in our Level 4 epilepsy center practice.

Methods: Charts of adult patients who were started on LAC from June 2009 to May 2010 were reviewed retrospectively, including clinic notes and laboratory results. Data abstracted included: age, seizure type, IQ, concomitant AEDs, titration schedule, final dose, serum AED levels, seizure control, adverse events.

Results: The first sixty patients were included in this early review; 3 had been in phase 3 trial with LAC. Patients were between ages 18-63. IQs were >90 in 17 (N), between 70-90 (LN) in 19; and <70 in 24 (LIQ). Seizure types were partial with or without secondary generalization in 55, primary generalized in 3 and mixed in 2. Doses were 100-800 mg/day. Co-medications were 1-4 other AEDs. Typically titration began at 25-50 mg per day, response assessed at 200 mg per/day, and increases made by response to therapy.

Five (8%) discontinued treatment: 1 for non-efficacy and 4 for adverse events (AEs). AEs included dizziness, nausea, vomiting, confusion, diplopia or blurred vision. These occurred in 15 patients. Eleven were on an AED with purported Na channel mechanism of action and 4 were on FBM. Two experienced weight increase. One reported depression, paranoia and panic. LAC blood levels ranged from 1.8-18.2 ug/ml, when available. There was no clear correlation between AE occurence and serum LAC level.

Three patients (5%) were seizure-free; 31 (52%) reported improved seizure control of at least 50% (responder group), 13 (27%) reported they were worse but only 4(7%)of these patients were worse due to seizures being worse, the other 9 having AEs. No notable change in seizures was reported in 13 (21%). In LIQ group of 24, 17 were responders (72%). In the responder group as a whole, doses were 200-700 mg/day with levels between 2.7-14.2 ug/ml. In the responder group, the median level was 9 ug/ml with median dose of 400, mean 380 mg/day. Side effects were reported at doses between 200-500 mg/day and LAC levels of 1.8-14.1 ug/ml.

Conclusions: LAC is added easily to most AED regimens. AEDs which act at the sodium channel may need to be down-titrated as LAC is added in order to reduce AEs and improve tolerability. Therapeutic efficacy in the group as a whole surpassed the phase 3 trial results with cognitively challenged individuals having an even greater response than the RR 40-46% at 400 mg/day in the trials.

1.312

A FIRST LOOK AT THE LANGUAGE AND DEVELOPMENTAL ABILITIES OF CHILDREN AGED THREE TO FOUR YEARS EXPOSED IN UTERO TO LEVETIRACETAM. ON BEHALF OF THE LIVERPOOL AND MANCHESTER NEURODEVELOPMENT GROUP AND THE UK EPILEPSY AND PREGNANCY REGISTER

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Rationale: Previously the Liverpool and Manchester Neurodevelopment group (LMNDG) reported that Levetiracetam (LVT) has little impact upon the developmental abilities of children, under the age of two years, exposed to this AED in utero. This is in contrast to some older anti epileptic drugs, such as Sodium Valproate (VPA), whereby impairment of development after in utero exposure has been reported.

The LMNDG reports its preliminary findings of children exposed in utero to LVT compared with children exposed in utero to VPA at three to four years of age.

Methods: Children exposed to either LVT monotherapy (n=40) or VPA monotherapy (n=32) were prospectively recruited from the UK Epilepsy and Pregnancy Register (UKEPR). Control children, born to women without epilepsy, not taking medication during pregnancy (n=125) were prospectively recruited from the LMNDG programme of research.

All children were assessed using the Griffiths Mental Development scales (2-8 years) and the Reynell Development Language Scales III. All mothers were assessed using the national adult reading test (NART) a standardised prediction of IQ.

Further information on maternal demographic and epilepsy variables was collected. ANOVA was conducted to compare group means. Regression analysis was then performed in order to control for confounding variables.

Results: Children exposed to LVT in utero did not differ significantly from control children on scores for the Griffiths Mental Development Scales or the Reynell Language Scales, with the exception of expressive language ability whereby significantly higher scores were seen in children exposed to LVT (p=0.04, m=52 vs m=46).

Children exposed in utero to LVT obtained significantly higher scores than children exposed to VPA for their locomotor skills (p=0.001, m=112 vs m=93), personal and social skills (p=0.018, m=116 vs m=103), and their hand and eye coordination skills (p=0.019, m=106 vs m=95).

Similarly, children exposed to VPA had lower scores than children exposed to LVT on their expressive language abilities (p=0.01, m=40.7 vs m=52). For comprehension of language abilities those exposed to VPA did not score significantly below those exposed to LVT (p=0.14, m=43 vs m=49), but they were significantly below control children (p=0.001, m=43 vs m=52).

Conclusions: The preliminary results reported here suggest that exposure to LVT in utero does not have a negative effect upon the neurodevelopment and language abilities of children aged three to four years.

VPA exposure, on the other hand is associated with a poorer level of ability in some cognitive domains. Data collection for this study is on-going.

1.313

RUFINAMIDE COULD A SECOD LINE FOR THE ADJUNCTIVE TREATMENT OF PARTIAL SEIZURES IN ADULTS?

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Rationale: Rufinamide is a triazole derivative, a novel antiepileptic drug (AED)which has been found to be effective in the treatment of drop attacks and partial seizures associated to Lennox - Gastaut Syndrome. Nevertheless efficacy of Rufinamide was demonstrated in five randomized placebo-controlled trials in patients with partial seizures. The aim of the study was to explore the efficacy of rufinamide as a second line adjunctive treatment of partial seizures in adult with focal epilepsy.

We aimed to describe a group of 10 patients with focal epilepsy who showed drug resistance to classic second line antiepileptic drugs.

Methods: This study was carried out in our Epilepsy Center.

We describe 10 adults patients (mean age 14,5) with focal epilepsy , who developed drug resistant epilepsy. Diagnosis of epilepsy was made according to the Commission on Classification and terminology of the International League against Epilepsy .

Patients were interviewed, and general and neurological physical examination was performed.

All underwent to prolonged awake and sleep polygraphic video-electroenecephalography study and high quality brain MRI. Initial dosage and titration of Rufinamide were at discretion of epileptologist according to medical need and considering changes in the pharmacokinetics associated to concomitants AED. Efficacy was evaluated by comparing the frequency of countable seizures at baseline (4 weeks before add-on of Rufinamide) with the frequency in the last 8 weeks of observation.

Results: six /ten patients were responders . Four patients experienced a greater 65% seizure reduction. Two patients showed a 25% seizure reduction , three of them not showed modifications in seizures frequency and one showed a gather reduction , but no frequency reduction.

Conclusions: Responder rates for patients with partial seizures was around 23% in the current opinions. But the patient population examined in previous literature showed mostly severe drug resistant epilepsy. Our sample, althought small, was selected basing on epilepsy resistance to two first line AED drugs. This data address us to puzzle that Rufinamide used as off-label treatment in not severely affected drug-resistance epilepsy showed higher responder rate , ranging from 25 to 65%of seizures reduction. Further study are required to clearly define patient population that could benefit by Rufinamide

1.314

TREATMENT OF INTRACTABLE EPILEPSY WITH RUFINAMIDE IN AN ACADEMIC MEDICAL CENTER

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Rationale: Recently, new anti-epileptic drugs have been introduced for intractable epilepsy syndromes including Lennox-Gastaut Syndrome (LGS). Among these is rufinamide, approved in November of 2008 for the adjunctive treatment of seizures in children 4 years or older, and adults. The objective of our study is to report our experience with rufinamide in a diverse patient population with LGS as well as other seizure disorders.

Methods: A retrospective chart review was performed on patients treated with rufinamide at Stony Brook University Medical Center from 1/1/2007 to 6/16/2010. Data was gathered including patient background, dosing, length of use, seizure type and frequency, epilepsy syndrome, VNS usage and adverse events.

Results: 33 patients were identified, 26 males and 7 females. Ages ranged from 3 to 52 years of age with 16 (48%) pediatric and 17 (52%) adults (>16 years old) with a mean age of 20 years. Mean dose was 28 mg/kg/day for the pediatric population and 1,483 mg/day for the adult population. Mean treatment duration was 332 days. All patients were on polypharmacy except for one. Number of other AEDs ranged from 0 to 6. Eight had a VNS implant. Indications for treatment were intractable epilepsy with poor seizure control. Seizures types were generalized tonic-clonic (26), atonic (9), myoclonic (11), partial (5), absence (5), juvenile myoclonic epilepsy (1), tonic (1), and infantile spasms (3). Seventeen met the criteria for LGS. Twenty-two patients (67%) experienced no adverse effects. Eleven patients (33%) experienced adverse effects necessitating discontinuation of rufinamide including anorexia (5), syncope (1), psychosis (1), headache (1), anxiety (1), and rash (1). One patient experienced a multi-organ system hypersensitivy reaction. There were no cases of SUDEP. Eighteen patients (55%) had improved seizure control during treatment. Although rufinamide is approved for LGS, we found a significant positive response in patients with other seizure disorders as well. EEGs before and during treatment were either unavailable for comparison or did not reveal unequivocal signs of electrographic improvement.

Conclusions: Rufinamide is a relatively new anti-epileptic drug approved for LGS in patients 4 years of age and older. In our study, rufinamide was well tolerated and efficacious in LGS and diverse epilepsy syndromes.

1.315

PRELIMINARY OUTCOMES WITH ADJUNCTIVE LACOSAMIDE IN PATIENTS WITH UNCONTROLLED PARTIAL-ONSET SEIZURES

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Rationale: Lacosamide (LCM) is licensed across Europe and in the USA as add-on therapy for the treatment of adults with partial-onset seizures. The drug may exert its effect by enhancing sodium channel slow inactivation and by binding to collapsin-response mediator protein

2. This prospective audit aims to ascertain outcomes with this new antiepileptic drug (AED) in everyday clinical practice.

Methods: To date, 76 patients (35M; 41F, aged 21-71 years [median 40 years]) with uncontrolled partial-onset seizures with or without secondary generalisation (monthly frequency range 1-300; [median 4]) have been started on LCM. Patients were taking a median of 1 AED (range 1-4), having previously tried 1-12 AEDs (median 2). After 12 weeks on stable AED doses, LCM was added with initial target dosing of 200-400mg/day. Review occurred every 6-8 weeks until 1 of 4 end-points was reached: seizure freedom for e”6 months on a given LCM dose; e”50% (responder) or <50% (marginal benefit) seizure reduction over 6 months compared with baseline on the highest tolerated LCM dose; withdrawal of LCM due to lack of efficacy, adverse effects, or both.

Results: An end-point has been reached by 50 (65.8%) of the 76 patients. Of these, 25 (50%) also took other sodium channel blocking drugs (sodium blockers; 14 carbamazepine, 5 oxcarbazepine, 4 lamotrigine, 2 phenytoin); 25 (50%) were taking AEDs with different mechanisms of action (see Table). Seizure freedom was achieved in 14 (28%), with a median LCM dose of 100mg/day (range 50-400mg/day). Of the seizure-free patients, 8 (57.1%) took other sodium blockers, with the remaining 6 (42.9%) taking different AEDs. Patients were more likely to become seizure-free when LCM was used as a first add-on (11 of 21, 52.4%), compared to a later treatment schedule (3 of 29, 10.3%; p=0.001). Fourteen (28%) patients could be classified as responders with a further 14 (28%) showing marginal benefit. LCM was withdrawn in 8 (10.5%) patients (3 lack of efficacy, 5 side effects), 4 of whom took concomitant sodium blockers. Problems leading to withdrawal in the 5 patients comprised sedation, ataxia, dizziness, agitation, tremor and headache. Only 2 (1 dizziness, 1 headache) were treated with other sodium blockers.

Conclusions: These preliminary data suggest that LCM appears an effective and well-tolerated adjunctive AED in patients with partial-onset seizures. Outcomes were no different when the drug was combined with other sodium blockers compared with patients taking AEDs with different mechanisms of action. Seizure freedom was more likely when LCM was used a first add-on compared to later in the treatment schedule.

Outcomes (percentages) with adjunctive lacosamide in patients taking sodium channel blocking antiepileptic drugs (AEDs) or AEDs with different mechanisms of action

IMAGE: tables/900135_T1.jpg

1.316

EFFICACY OF VIGABATRIN IN CONTROLLING CLINICAL SEIZURES FOR PATIENTS WITH INFANTILE SPASMS: CLINICAL EXPERIENCE FROM THE CHILDREN’S HOSPITAL OF MICHIGAN

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Rationale: Vigabatrin (VGB), an antiepileptic drug (AED), was approved in August 2009 as monotherapy for patients 1 month to 2 years of age with infantile spasms (IS). VGB works by inhibiting GABA transaminase. Diagnosis of IS requires a substantial degree of clinical suspicion, and, if left untreated, the disease can have dire neuro-developmental consequences. IS is frequently refractory, and often requires therapy trials with several AEDs before one is found that controls seizures. In this retrospective analysis, we investigated our clinical experience with VGB for IS.

Methods: The Children’s Hospital of Michigan is a major referring center for IS patients who require surgical evaluation, especially for those with intractable spasms. We employed records from our IS database of 263 patients treated 1999-2009. Many patients have been receiving VGB, while others have received alternative AEDs, including hormonal therapy (i.e., ACTH). We performed a retrospective review of data for our patients with IS via our electronic health records (EHRs), as well as follow-up telephone calls to patients’ parents/caregivers, to assess the efficacy of VGB in controlling patients’ clinical seizures. We assigned subjective ratings of 1) poor or no control of seizures with VGB, 2) moderate to good control of seizures with VGB, and 3) excellent control of seizures with VGB for each patient as a way of assessing VGB’s effect in our large cohort of real-world patients.

Results: As of June 2009, of the 263 patients in our IS database, 130 (49.4%) had been receiving VGB. Of these 130, 71 (54.6%) had achieved excellent seizure control, (21.5%) had achieved moderate to good control, and 31 (23.8%) had poor or no seizure control with VGB. The percentage of VGB patients achieving excellent control versus those achieving poor or no control was highly statistically significant ($p<0.0001$, chi-square test). In addition, a PubMed search indicated no publications of single-arm cohorts with as many patients as included in this cohort.

Conclusions: Our results indicate that VGB is effective in clinically controlling seizures in a large cohort of patients with IS. To prevent a devastating neuro-developmental sequalae of untreated IS, VGB should be initiated early in the clinical course of IS. However, judicious use of VGB is essential, and careful visual field testing should be conducted regularly to assess potential retinopathy associated with VGB. To our knowledge, this is the largest single-center cohort of IS patients treated with VGB, and these patients will be tracked to assess long-term outcomes.

1.317

LACOSAMIDE IN REFRACTORY PEDIATRIC EPILEPSY

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Rationale: Lacosamide (Vimpat®) is the newest generation anti-epileptic drug that acts on voltage-gated sodium channels to enhance slow inactivation. It is currently FDA approved for adults e”17 years of age for partial-onset seizures. Given its favorable efficacy, pharmacokinetic, and safety profile in adults, we believe it may be a useful anti-epileptic drug for children with refractory epilepsy.

Methods: This is a single-center, prospective, ongoing, open-label study. Hospital IRB approval was obtained. Pediatric patients that were started on lacosamide after June 2009 as an adjunct for refractory epilepsy with various seizures types were followed. Inclusion criteria were children under the age of 18 and those who were refractory to multiple other anti-epileptic agents. Seizure type and frequency, drug dosage, duration, and adverse events were documented at baseline and at routine follow-up visits.

Results: The age range of eleven patients was 20 months to 17 years (mean age 10.6 years). There were 7 males and 4 females. Diagnoses included localization-related epilepsy, Lennox-Gastaut Syndrome, and cryptogenic generalized epilepsy. The average number of seizure types

per patient was 1.36. These included generalized-tonic clonic, atonic, tonic, and complex-partial seizures with or without secondary generalization. The average number of anti-epileptic agents that patients were on was 2.2. On average, patients had failed 6.4 other anti-epileptic agents, including the ketogenic diet and the vagus nerve stimulator. Patients were started on a moderate dose of lacosamide and generally titrated up weekly to an average dose of 7.3/mg/kg/day (range 3.2 to 12.8 mg/kg/day). Average length of initial follow-up was three months. Preliminary results of this prospective on-going trial showed lacosamide was effective in six of 8 patients with complex partial seizures. Two patients remain seizure-free. Two patients resulted in seizure reduction greater than 90%. Two patients had seizure reduction greater than 50%. Lacosamide was not found to be effective in the three remaining patients with generalized seizures (tonic-clonic, tonic and atonic seizures). Three patients were discontinued for lack of efficacy and/or adverse events, which included headache and increased seizure frequency.

Conclusions: Lacosamide is generally effective and well tolerated in pediatric patients with refractory partial-onset epilepsy, usually as an adjunctive therapy. In this prospective, on-going study, six of eight pediatric patients with refractory complex-partial seizures responded well to the addition of lacosamide. Its efficacy in other seizure types remains to be determined.

Pediatric Patients on Lacosamide

IMAGE: tables/908231_T1.jpg

1.318

INDIVIDUAL VERBAL MEMORY OUTCOME 2 AND 10 YEARS AFTER TLR: A LONGITUDINAL CONTROLLED STUDY

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Rationale: There is an extensive individual variation in memory outcome after temporal lobe resection (TLR) for epilepsy. Considerable efforts have been made to identify specific risk factors for postoperative memory decline. The aims of this study were to describe individual verbal memory changes after TLR and to explore risk factors for postoperative early and late verbal memory decline.

Methods: Fifty patients who had undergone TLR (23 in the speech dominant temporal lobe, DTL; 27 in the non-dominant temporal lobe, NDTL) were tested preoperatively, 2 and 10 years postoperatively. Twenty-three healthy controls were assessed at baseline and at corresponding test intervals. Learning and delayed recall of a wordlist and immediate and delayed recall of word-pairs were used for assessing verbal memory. On the basis of how many of the four verbal memory variables that had changed according to cut-off scores of the reliable change indices (RCI) 90% confidence interval (CI) of the controls, individual changes were categorized as follows: 'Declinee"1' (e"1 negative and no positive change); 'Declinee"2' (e"2 negative and no positive changes); 'Improvemente"1' (e"1 positive and no negative change); 'Improvemente"2' (e"2 positive and no negative changes).

Results: In the whole patient group fewer patients had Declinee"2 at 10-year (14%) compared with 2-year follow-up (28%). This held true both for the DTL (10-year: 26.1%, 2-year: 43.5%) and the NDTL group (10-year: 3.7%, 2-year: 14.8%). A similar pattern was seen for the NDTL group regarding Improvemente"2 (10-year: 29.6%, 2-year: 18.5%). Five potential prediction variables were selected based on earlier findings and availability of data in the patient series: laterality; baseline verbal memory; baseline verbal IQ; baseline chronological age and cortical dysgenesis in the resected tissue. Intact baseline verbal memory (p=0.004), DTL resection (p=0.009), and older age at baseline (p=0.017) were identified as predictors of verbal memory Declinee"1 2 years after surgery, while only DTL resection was a predictor at 10 years (p=0.001).

Conclusions: Our findings indicate an extensive individual variability in verbal memory outcome after TLR, but also a partial recovery for some patients in verbal memory function between 2 and 10 years after surgery. Factors that are important predictors for verbal memory decline at earlier stages may be less important at long-term follow-up. The only remaining risk factor for impaired verbal memory at the long-term follow-up was DTL resection.

1.319

NEUROPSYCHOLOGICAL TESTING OF HISPANIC SEIZURE PATIENTS WITH COMPREHENSIVE TESTING DEVELOPED AND NORMED ON HISPANIC SAMPLES

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Rationale: Neuropsychological testing helps in pre-surgical treatment planning by assisting in lateralization of the seizure focus. Previous research with English speakers shows that tests of naming and verbal memory are significantly worse in patients with left hemisphere (LH) onsets vs. right hemisphere (RH) onsets, but findings with Hispanic patients using screening batteries (e.g., the Neuropsychological Screening Battery for Hispanics, NeSBHIS) have not been promising. The current study examines the utility of more extensive standardized tests developed for and normed on Hispanic samples in differentiating patients with LH vs. RH seizure onsets.

Methods: All of the neuropsychological reports on Hispanic pre-surgical epilepsy patients from 2003 to 2009 performed at the Northeast Regional Epilepsy Group were reviewed. Subjects were all self-identified as Hispanic and spoke Spanish as their primary language, and were all tested only in Spanish. All patients with unambiguous lateralized partial epilepsy confirmed by Video EEG monitoring and MRI and who proceeded to surgery were selected (n=38). Patients were administered the Ponton-Satz Naming Test, WHO/UCLA Auditory Verbal Memory Test, the Brief Intellectual Ability quotient (BIA) from the Bateria III Woodcock Munoz (BIA) & Achievement subtests (reading comprehension, spelling and mathematical operations), Continuous Visual Memory Test, Phonemic (FAS) and Categorical (Animal) Fluency, Grooved Pegboard, and mood inventories (Beck Anxiety Inventory and Beck Depression Inventory-Second Edition). Student's t-test for the major scores from each test was performed for LH vs. RH onsets.

Results: Descriptive statistics of the sample yielded a mean (SD) age at testing=42.2 (15.7), age at onset= 20.1 (19.3), education= 10.1 (3.0), 25 women, and 5 non-right-handers. The results showed that LH onset patients performed significantly worse than RH onset patients for the BIA Verbal Ability (78.8 v. 88.4, p=.009) and Verbal Comprehension (78.9 v. 90.3, p=.004) scales. The Ponton-Satz was also significantly different between LH v. RH onset patients (14.8 v. 20.9, p=.001).

Conclusions: Use of a comprehensive battery of neuropsychological tests developed for and normed on Hispanic samples proves useful in lateralizing patients with left vs. right hemisphere seizure onsets, equivalent to test batteries for English speaking patients. Prior negative findings with the NeSBHIS may relate to the use of only brief screening measures (average of 90 minutes versus a 3-4 hour assessment) or outdated (e.g., Escala de Inteligencia Wechsler para Adultos-EIWA) subtests compared to more thorough batteries normed on a more current and broad sample of Hispanics.

1.320

WADA RISK CLASSIFICATION FOR MEMORY LOSS RELIABLY PREDICTS POSTOPERATIVE VERBAL MEMORY DECLINE IN LEFT TEMPORAL LOBECTOMY PATIENTS

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Rationale: Investigations into the ability of Wada testing to accurately predict memory loss after anterior temporal lobectomy have yielded contradictory results. Although conflicting results are secondary to a variety of methodological dissimilarities across studies, important factors include inadequate sample sizes and differences in how Wada memory was assessed. To address these deficiencies, we evaluated the memory test performances of temporal lobectomy patients before and after surgery after classifying their risk for memory loss using the most common Wada memory assessment method; viz., where a predetermined number of discrete stimuli were presented during the period of drug effect, and then memory for the stimuli was assessed after hemispheric anesthetization resolved.

Methods: 94 (54 left, 40 right) adult temporal lobectomy patients were classified into 1 of 3 risk groups after Wada memory testing in both hemispheres. There were 46 males and 48 females with a mean age of 32.6, 12.3 years of education, FSIQ of 88.17, and seizure duration of 16.8 years. High risk patients (N=48) showed either no, or reversed (contralateral injection > ipsilateral injection), memory asymmetry and also had normal memory after contralateral injection. Mild risk patients (N=25) showed memory asymmetries either in the correct direction (contralateral < ipsilateral) with normal contralateral memory or no asymmetry (<3/8 memory items) but failed both injections. No risk patients (N=21) displayed memory asymmetries in the correct direction and failed contralateral injection. Pre- and post-surgical verbal and visuospatial neuropsychological memory testing was conducted using the Selective Reminding Test (SRT), WMS Logical Memory (LM), WMS Paired Associate Learning (PA), WMS Faces, and Rey Complex Figure delayed recall (RCF).

Results: Left High Risk patients showed significant pre-to-postsurgical declines on SRT and PA with significant interaction effects (RTLs improved postoperatively) on both measures. Left Mild Risk patients displayed significant pre-to-postsurgical decline only on PA again with a significant interaction effect for PA only (RTLs improved). There were no significant postoperative changes on any of the verbal or nonverbal memory tests in the No Risk group. There was no significant pre-to-postoperative deterioration among right TLs on any of the 5 memory tests.

Conclusions: Wada testing appears to have reasonably good predictive validity in determining degree of risk for postoperative verbal memory impairment in left ATLs when classification is based upon Wada memory asymmetries in conjunction with memory failure after contralateral amobarbital injection. Similar studies will need to be conducted on fMRI memory activation paradigms before Wada testing is replaced by fMRI in the preoperative evaluation for epilepsy surgery.

1.321

INDIVIDUAL DIFFERENCES IN TPM-INDUCED COGNITIVE PERFORMANCE AS A FUNCTION OF TPM PLASMA LEVELS

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Rationale: Topiramate (TPM) is indicated for partial onset seizures and migraine prophylaxis, and is used to manage obesity, bipolar disorder, and pain. Unfortunately, individual patients on TPM manifest varying degrees of cognitive impairment, often reporting significant language and speech problems. In order to characterize TPM-induced effects on spontaneous speech and their relationship to individual drug pharmacokinetics, we studied the effects of a single, 100 mg dose of TPM on a brief neuropsychological battery (NP) in healthy adults. A novel semi-automated language and speech analysis (SALSA) was used to detect drug-induced changes.

Methods: Eleven healthy volunteers were included in the analysis of a crossover of TPM (100mg), lorazepam (LOR: 2mg), and placebo (PL). LOR, a benzodiazepine, was chosen as a comparator drug. The NP included the COWA, a test of generative verbal fluency, a picture description (PD) test, used to elicit spontaneous speech, and the MCG Paragraph Memory (MCG) test, where the subject is asked to recall a short story presented verbally twice during the NP (MCG1&MCG2). Baseline measures were collected on the first and last study sessions and averaged to account for practice effects. Subjects were randomized to TPM, LOR, or PL with at least a one-week washout period between each session. The NP, recorded for speech analysis, was given 1hr after dosing, and lasted approximately 1hr. A single blood draw was taken immediately after NP testing; TPM and LOR concentrations were measured using a validated LCMS method. Change in individual test performance was calculated by subtracting the average baseline test score from the score during drug (or placebo) treatment divided by the average baseline.

Results: Individual TPM plasma levels varied from 0.23-2.81ug/mL. The number of dysfluencies generated from the PD during the TPM arm and measured using SALSA was highly correlated with TPM levels (Spearman's r=0.65, p=0.03). COWA failed to reveal any relationship between verbal fluency and drug plasma levels. SALSA also discriminated between the effect of TPM and LOR on individual performance on MCG2. The number of correct words recalled while on TPM was correlated negatively with TPM levels (Spearman's r=-0.75 p=0.007), but positively with LOR levels (r=0.76 p=0.007).

Conclusions: This is the first study to demonstrate a significant association between TPM plasma levels and individual measures of verbal fluency and recall. SALSA, in combination with a PD task proved more sensitive than traditional methods of analysis to TPM-induced changes in verbal fluency. These data facilitate our understanding of the heterogeneity of the cognitive response to a single dose of TPM and underscore the limitations of only taking into account drug dosage when clinically assessing severity of TPM's effects on speech. Given its ability to differentiate between the effects of TPM and LOR on story recall, we expect SALSA to yield further insights into drug-induced effects on cognitive function.

1.322

STUDYING CORRELATIONS BETWEEN WHITE MATTER AND NEUROPSYCHOLOGICAL PROFILE IN TEMPORAL LOBE EPILEPSY USING DIFFUSION TENSOR IMAGING

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Rationale: Temporal lobe epilepsy (TLE) has been demonstrated to be associated with extensive anatomical abnormalities (involving both temporal and extratemporal grey and white matter) as well as extensive neuropsychological deficits. The structural basis for the observed neuropsychological deficits (in particular the role of white matter abnormalities in functional deficits) remains poorly understood. The purpose of this study was to use diffusion tensor imaging (DTI) to investigate the relationship between the integrity of cerebral white matter and neuropsychological function in TLE patients.

Methods: Twenty-two TLE patients, including eight non-lesional patients and fourteen with unilateral mesial temporal sclerosis, were studied. DTI, FLAIR DTI, and hippocampal T2 relaxometry data were obtained using a 1.5T scanner. Spearman's correlations were performed between fractional anisotropy (FA) of the bilateral fornix, cingulum, external capsule, uncinate fasciculus, as well as the genu and splenium of the corpus callosum, and hippocampal T2 versus neuropsychological tests of verbal and nonverbal memory along with more global measures (such as IQ).

Results: The most striking correlations were observed for the left fornix, demonstrating significance with measures of both verbal and non-verbal memory (Recognition Memory for Words: $r = 0.538$; $p = 0.012$, and Continuous Visual Memory Test: $r = 0.519$; $p = 0.013$) as well as more general cognitive scores (Full Scale IQ: $r = 0.615$; $p = 0.004$, Performance IQ: $r = 0.611$; $p = 0.003$, and Processing Speed Index: $r = 0.668$; $p = 0.001$). Significant associations were also observed between left hippocampal T2 and verbal memory tests (Recognition Memory for Words: $r = -0.452$; $p = 0.040$, and Auditory-Verbal Learning Test: $r = -0.561$; $p = 0.007$). Other significant correlations include the right external capsule and genu with the Controlled Oral Word Association Test: $r = 0.477$; $p = 0.025$, and $r = 0.433$; $p = 0.040$, respectively. FA of the right fornix, left external capsule, bilateral cingulum, uncinate fasciculus, and splenium failed to correlate significantly with any of the neuropsychological tests.

Conclusions: Our findings suggest that integrity of the left fornix specifically is an important anatomical correlate of both specific (verbal memory) as well as more global (IQ) cognitive function in TLE patients.

1.323

LEARNING WORDS AND REMEMBERING DESIGNS: UNDERSTANDING LEFT AND RIGHT MEDIAL TEMPORAL LOBE FUNCTION IN EPILEPSY

Sarah Banks, V. Sziklas, J. Bellerose, D. S. Ladowski and M. Jones-Gotman (Montreal Neurological Institute, Montreal, Canada)

Rationale: fMRI memory paradigms may be useful in assessing functionality of tissue prior to resection for intractable temporal lobe epilepsy (TLE). To date, verbal memory fMRI tasks have been somewhat useful in demonstrating function of the left hippocampus and nearby structures, but attempts at investigating function of the right medial temporal structures with nonverbal tests have had less encouraging results. Furthermore, recent research suggests that the left and right hippocampi may have different roles based on how novel the encoded stimuli are, e.g., the left hippocampus appears more sensitive to never-before-seen stimuli. We identified aspects of verbal and nonverbal memory tests that resulted in increased activation in the left or right hippocampi, respectively, in healthy individuals. The present study compares activation in patients with TLE to that of healthy subjects on these tasks and investigates whether individual activation profiles can be useful in presurgical assessment.

Methods: We used two matched tests, each comprising initial encoding, initial recognition, second encoding, second recognition and delayed recognition. Targets were presented in a block design with appropriate baseline stimuli. Stimuli were designed to maximize specificity: verbal items were pronounceable pseudowords (difficult to associate with an image) and nonverbal items were abstract designs (not easily named). We used 3T MRI to collect high-resolution images. Subjects were patients with unilateral TLE and age and education matched healthy volunteers. After spatial preprocessing, data were analyzed on the group level. Contrasts in activation were assessed within a masked area including the hippocampus, amygdala and parahippocampal region. Percent signal change in the hippocampi and parahippocampal gyri were calculated and used to assess results on an individual basis.

Results: Healthy subjects showed isolated hemispheric MTL activation in particular material specific conditions: For verbal information, the left hippocampus was more active during initial compared to second encoding; for nonverbal information, the right hippocampus was more active during second retrieval compared with first. Patients showed reversals in the regions activated: Left TLE patients showed increased right activation during encoding of never-before-seen verbal information but performed worse on this test than controls, and patients with right TLE showed increased left activation on the second attempt at recognizing nonverbal information with poorer (although not significantly so) task performance.

Conclusions: Our findings suggest a complex interaction between material specificity, familiarity and memory process in left and right MTL function. Using contrasts reflecting this interaction, we demonstrated apparent reversals in lateralization in patients with unilateral TLE compared to healthy individuals, without preservation of normal function. This approach may be useful in identifying the eloquency of tissue in individuals during preoperative assessment.

1.324

PHYSIOLOGICAL RESPONSE TO EMOTIONAL FACES IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Rationale: In various neurological and psychiatric disorders, deficits in emotional response are associated with abnormalities in amygdala functioning. Although emotion recognition itself is often performed well, individuals with neurological or psychiatric conditions are often found to have abnormal autonomic response to emotional stimuli, however this has rarely been assessed as a function of amygdala atrophy. The purpose of this study was to examine the relationship

between skin conductance responses and amygdala volume to emotional stimuli in patients with medial temporal lobe damage compared with healthy volunteers.

Methods: The study involved two tasks: an implicit and an explicit task. The implicit task was presented first and involved viewing a series of 24 faces that expressed one of six emotions (happiness, fear, sadness, anger, disgust, and neutral). Each face was presented with a choice of two ages and the subject had to decide which number best represented how old they thought the person in the picture was. In the explicit task, the subjects were presented with similar pictures but for this task they had to choose which of two emotion labels best represented the face on the screen. During both tasks, electrodes were attached to the subjects' fingers on both hands to measure skin conductance while responses were spoken. Bilateral recordings are not the norm in this field, but in patients with unilateral temporal lobe pathology, subtle differences related to lateralization may be relevant. Following completion of the tasks, subjects underwent a high resolution structural MRI scan in a 3 Tesla magnet. After appropriate preprocessing of the scans, amygdalae were segmented manually and volumes calculated using inhouse software.

Results: Contrasting with the classic view that skin conductance only distinguishes valenced stimuli from neutral, the response profile to different emotions in our healthy volunteers showed an interesting pattern, specifically with the right hand. We found higher responses to "fight or flight" emotions such as fear and disgust, especially when the data was presented explicitly. In comparison, patients with epilepsy primarily affecting their left hemisphere showed atypical responses: Compared with their healthy counterparts they showed relatively greater response to faces depicting sadness in our implicit task, and reduced response to faces depicting disgust in the explicit task. As would be expected, amygdala volume in healthy control subjects was unrelated to skin conductance response to emotional faces.

Conclusions: These initial results point to differences in reaction to certain emotions in patients with subtle damage to the medial temporal lobe. The differences most likely reflect structural and functional changes in the temporal lobe emotion circuitry. The nature of the differences, specifically heightened reaction to sad faces in patients with left sided pathology, may underpin the exaggerated prevalence of depression in this patient population.

1.325

NON-VERBAL COMMUNICATION IN PATIENTS WITH EPILEPSY

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Rationale: Effective social interaction depends in part on the ability to accurately interpret certain aspects of non-verbal communication. For instance, facial expression can drastically change the intended meaning of a statement in a conversation. Multiple lines of evidence suggest that specific networks spanning the frontal and temporal lobes of the brain support this type of non-verbal communication. Coincidentally, these regions are frequently implicated as the cause of focal epilepsy. Deficits in memory, language, and psychiatric function in patients with focal epilepsy have been closely investigated. In contrast, only a handful of investigators have addressed problems with non-verbal communication in these patients. Our hypothesis is that patients with refractory temporal and frontal lobe epilepsy have difficulties with perception of certain aspects of non-verbal communication.

Methods: To test our hypothesis, we administered a video based neuropsychological instrument called The Awareness of Social Inference Test (TASIT) which evaluates certain aspects of non-verbal communication to a cohort of 19 patients with medically refractory localization-related epilepsy. We compared the results to a published cohort of normal subjects using a one-sample t-test.

Results: Patients with epilepsy had difficulty with emotional recognition compared normal controls (mean of 18.1 compared to mean of 24.86; $p<0.001$). Patients with epilepsy scored lower for recognition of sarcasm compared to normal controls (mean of 42.3 compared to a mean of 54.1; $p<0.001$). Patients with epilepsy had difficulty with differentiating insincere responses from sarcastic responses (mean 43.7 compared to a mean of 55.6; $p<0.001$).

Conclusions: Our findings support the idea that focal epilepsy is associated with deficits in perception of non-verbal communication. The etiology of social cognitive disturbances in patients with epilepsy may be due to underlying neuropathology, due to ongoing seizure activity itself, or secondary to relative social isolation of patients with epilepsy. Further planned work includes addition of neuropsychological instruments which measure general intellectual function and obtaining an original control group. Strategies that improve non-verbal communication may improve the quality of life of patients with focal epilepsies.

1.326

CORTISOL IS NOT RELATED TO DEPRESSIVE SYMPTOMS OR MESIAL TEMPORAL INTEGRITY IN PATIENTS WITH MEDICALLY INTRACTABLE TEMPORAL LOBE EPILEPSY

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Rationale: Research on patients with major depressive disorder has demonstrated that elevated cortisol levels are associated with memory impairment and hippocampal atrophy in these patients. Temporal lobe epilepsy (TLE) is often associated with depression, memory dysfunction, and hippocampal atrophy. However, the relationships among these factors within TLE patients have not been well-delineated. This study was designed to prospectively examine the relationships among late night salivary cortisol (NSC) levels (an index of hypercortisolism) and depressive symptoms, memory performance, and hippocampal volumes in patients with medically intractable TLE.

Methods: This prospective study included twenty-four adults with well-characterized medically refractory TLE (right=11; left=12; bitemporal=1), as defined by concordant seizure semiology as well as interictal and ictal EEG recordings. Mean age was 39.71 (SD=11.56) and education was 14.04 years. Mean age of seizure onset was 26.33 years (SD=12.58), and duration of epilepsy was 13.29 years (SD = 9.92). All patients provided samples to measure NSC and completed measures of mood, anxiety, and memory (objective and subjective). MRI-based volumetric analyses of the hippocampi were also conducted.

Results: Bivariate correlations were calculated to examine the strength of the relationship between cortisol level and mood, anxiety, memory, and hippocampal volume. Unexpectedly, cortisol levels were not related to symptoms of depression or anxiety, subjective memory ratings, objective memory performance, or hippocampal volume (range r = -.06 to -.32).

Although no significant relationships were observed between cortisol and the variables of interest in this study, there were several significant relationships among other study variables. Objective memory performance on the Rey Auditory Verbal Learning Test (RAVLT) was related to both left (r = .45) and right hippocampal volumes (r = .48). Subjective memory complaints were not related to objective memory performance, but were strongly correlated with symptoms of depression [Personality Assessment Inventory (PAI) Depression Subscale r = -.52; Center for Epidemiological Studies - Depression Scale (CES-D) r = -.46] and trait anxiety as assessed by the State Trait Anxiety Index (r = -.44). Additional regression analyses revealed that depression scores, as assessed by the CES-D and the PAI, predicted subjective memory ratings on some measures ($p < .05$). There was also a trend for the PAI Depression subscale to predict objective memory performance on the RAVLT ($p = .07$).

Conclusions: Results suggest that NSC is not related to symptoms of depression or anxiety or to functional and structural integrity of the mesial temporal lobe in patients with intractable TLE. However, consistent with existing literature, objective memory was related to hippocampal volume, and subjective memory was related to mood and anxiety symptoms.

1.327

A COMPREHENSIVE FMRI LANGUAGE BATTERY DISCLOSES EXTENSIVE INTER- AND INTRAHEMISPHERIC LANGUAGE REORGANIZATION IN EPILEPSY WITH LEFT MESIAL TEMPORAL SCLEROSIS

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Rationale: Functional Magnetic Resonance Imaging (fMRI) has been used for preoperative brain mapping in patients with epilepsy due to hippocampal sclerosis (HS). The use of more than one language paradigm allows a more robust identification of language areas. We evaluated language activation patterns in patients with left temporal lobe epilepsy with HS, with four different language paradigms assessing different language aspects.

Methods: Seven right handed patients with epilepsy secondary to left HS and seven right handed normal controls underwent an fMRI study using four distinct paradigms: word generation (WG), visual confrontation (CN) and written sentence responsive naming (RN), as well as phonologic and semantic language decision (LD). Data were collected with a 3T MRI scanner with compressed GRE EPI BOLD images (40 ACPC oriented slices, 3.3mm isometric voxels, TR=4s, TE30ms/ FA90). All paradigms were block designed, each with a five minutes' duration. Data analysis was performed with XBAM (http://www.brainmap.co.uk), using a nonparametric statistical inference approach. Patients and controls activation maps were compared with ANOVA, with a significance level of $p<0.05$.

Results: Both patients and controls group maps showed increased BOLD effect in the frontal gyri (bilateral for WG; and left for all others), temporal-occipital (bilateral for WG and RN and left for all others), SMA/cingulate gyrus, and left parietal cortex. On WG, the patients group showed an increased number of activated regions in the right hemisphere, and an overall decreased BOLD effect in the homologous regions on the left side. On VCN, the patients group showed increased activation in the right temporal-parietal and right parietal regions, posterior cingulate and left middle frontal gyrus, and a reduced activation in the left middle frontal, left inferior parietal gyri, right inferior temporal gyrus, as well as right anterior cingulus and right frontal-basal region. On RN, the patients group map showed decreased number of clusters in all the above listed regions; and an increased number of clusters in right inferior and middle frontal gyri, bilateral temporal regions and left cerebellum. On LD, the patients group map showed increased number of clusters in the right hemisphere (inferior and middle frontal, superior temporal and inferior parietal regions) and an overall decrease in the BOLD effect at the homologous clusters, in the left temporal-parietal regions and right temporal pole, right frontal-basal region and right inferior frontal gyrus.

Conclusions: We found a consistent pattern of language network reorganization in TLE-MTS throughout the tasks, with decreased activation of left hemisphere language related regions, with increased activation of areas neighboring language areas and extensive activation of contralateral homologous brain regions. Mesial temporal lobe epilepsy associated with mesial temporal sclerosis appears to cause extensive at-distance reorganization of the language network.

IMAGE: images/907197_A.jpg

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MODIFICATION AND IMPROVEMENT OF AN EXISTING GROUP TREATMENT FOR PSYCHOLOGICAL NON-EPILEPTIC SEIZURES

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Rationale: In 2002, two of the authors (CM Zaroff, L Myers, et al, 2004) designed a group treatment for psychological non-epileptic seizures (PNES). Seven patients completed the treatment and were assessed on seizure frequency, stress management strategies, trauma, anger, quality of life and dissociative symptoms. Although there was no change in terms of seizure frequency post-treatment, there were changes in dissociative symptoms and quality of life.

The present treatment model utilized this as a starting point, modified pre and post assessment and further refined the actual treatment program.

Methods: Assessment: In 2002, pre and post measures included the Davidson Trauma Scale (DTS), Curious Experiences Survey (CES), Quality of Life in Epilepsy-31 (QOLIE-31), State Trait Anger Expression Inventory (STAXI-2), and the Coping Inventory for Stressful Situations (CISS). In the present format, the QOLIE-31, STAXI and CISS were maintained and the Toronto Alexithymia Scale (TAS) was added. The CES and DTS were replaced by the Trauma Symptom Inventory (TSI). Seizure frequency continued to be monitored weekly.

Treatment: In 2002, treatment was completed over 10 weeks. The following topics were addressed in this order of presentation: PNES, anger, trauma and abuse, depression and anxiety, somatization tendencies, quality of life, paths toward health, stress coping techniques, and review. The current treatment further refined the targets and shifted the order of topics: PNES, PTSD, anxiety, depression, healing PTSD, anxiety reduction 1, anxiety reduction 2, assertiveness training, complementary healthy behaviors, positive psychology, alternative treatments, review). The guiding premise that greater understanding about one's illness provides greater control remains prevalent. However, the new model concentrates increasingly on anxiety management (breathing and visualization strategies are practiced), post-traumatic healing (targeting avoidance behaviors, keeping of gratitude diary) and assertiveness training (anger management and script writing).

A comparative analysis of results from pre- and post- self-report measures was performed to determine the effectiveness of group treatment upon the completion of the 12-session period. Seizure frequency was also determined.

Results: Nine of the 14 patients completed the treatment program. As for seizure frequency, 3 patients became seizure free, one was seizure free at the outset, two patients went from weekly to monthly seizures and one went from "every 2 hours" to weekly. Two experienced no change. The mean TAS score fell 14 points following treatment. The mean score on the CISS Emotion scale went from high average to average. Overall quality of life improved post treatment in comparison to a normative sample.

Conclusions: Refinements made to the preliminary PNES group treatment model resulted in notable improvements, including seizure elimination or reduction. A positive trend regarding quality of life and alexithymia were also noted. Two month follow up revealed that gains had been maintained.

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COGSCREEN IN TEMPORAL LOBE EPILEPSY PATIENTS VERSUS CONTROLS

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Rationale: The CogScreen is a computer-administered and scored instrument which rapidly assesses deficits or changes in cognitive domains including attention, immediate- and short-term memory, and reaction time. It is widely used in clinical trials and in military and industrial research. It has not been used previously to evaluate cognition in epilepsy patients. We compared the baseline CogScreen results in adult temporal lobe epilepsy patients enrolled in a clinical trial with healthy controls in order to assess its utility in this population.

Methods: The initial CogScreen data of well-controlled adult epilepsy patients with an estimated intelligence quotient of >70 using the Wechsler Test of Adult Reading were compared with healthy control subjects. The two groups were matched for age, gender and level of education, however, the control group took no centrally-acting medications. We used six CogScreen subtests based on the use of the CogScreen in previous research. Mean number of items completed, reaction time and accuracy for the six selected subtests were compared between patients and controls with Mann-Whitney U.

Results: Six subjects and eight controls enrolled. The six subjects had rare seizures and none in the two days prior to the CogScreen test. There were no baseline differences in age (subjects 49 years, controls 43 years) gender (80% women in both groups) and years of education (subjects 16 years, controls 18 years). Subjects were taking between 1 and 3 antiseizure medications, with a median of 3. Controls were not taking any centrally-acting medications; 6 of 8 were not taking any medications. The CogScreen subtest showing a difference between groups was symbol digit coding. There were significant differences in the number of items completed and reaction time between the groups; p=0.014 and p=0.020 respectively. For the control group, the mean number of items completed was 48 and the mean reaction time was 1674 milliseconds. No subject achieved these numbers of items completed or this reaction time; further the mean the mean number of items completed was 33 and the mean reaction time was 2440 milliseconds. There was no difference in the accuracy however.

Conclusions: The symbol-digit coding was significantly different between temporal lobe epilepsy patients and controls. This finding is not surprising given that Symbol-digit coding among the most sensitive of all neuropsychological tests to any cognitive dysfunction. Its inclusion in the CogScreen battery may be useful for determining cognitive dysfunction in an epilepsy patient sample. The fact that it is computer self-administered may prove to be cost-effective in applications such as clinical drug trials. A larger sample size may reveal further differences in the comparison groups.

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PSYCHOGENIC NONEPILEPTIC SEIZURE AND PSYCHOGENIC MOVEMENT DISORDER PATIENTS: ARE THEY THE SAME?

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Rationale: The objective of the study is to compare the psychosocial profiles and demographics of patients with psychogenic nonepileptic seizures (PNES) with psychogenic movement disorders (PMD). Psychological dysfunction is present in both PNES and PMD patients. Though PNES and PMD are usually studied separately, our hypothesis is that the psychosocial profiles and demographics are similar despite different clinical presentations.

Methods: PNES patients from the University of Maryland Epilepsy Center (n=33) and PMD patients from the Movement Disorders Center (n=104) completed the SF-12 Health Status Survey, the Brief Symptom Inventory-18 (BSI-18), the Lorig Self Efficacy Scale, and a demographic questionnaire. PNES and PMD data were compared with standard t-tests.

Results: Both PNES and PMD groups scored low on SF-12 Physical Health (mean 37.5 and 34.8, p=0.38) and Mental Health (mean 44.4 and 43.4, p=0.70) quality of life. Both groups had high BSI somatization (63.6 and 63.1, p=0.78), depression (54.8 and 55.6, p=0.76), and anxiety (57.6 and 56.0, p=0.49) scores. Both PNES and PMD groups had similar Self Efficacy scores in subsets of their perception of their ability To Manage Disease (11.8 v. 11.5, p=0.55), Do Chores (6.3 v. 6.5, p=0.70), Do Social Activities (4.5 v. 4.1, p=0.16), Manage Symptoms (10.0 v. 9.4, p=0.25), and Exercise (6.6 v. 6.0, p=0.17).

Both groups had similar rates of marriage (66.7% and 69.6%, p=0.83), employment (45.4% and 44.4%, p=1.00) and level of education (39.4% and 41.4%, p=1.00). Differences between the groups were that PNES patients were more likely to be female than PMD patients (87.9% vs. 67.0%, p<0.05) and PNES patients were more likely to report episodic symptoms than PMD patients (100% vs. 66.7%, p=0.0008). In addition, the mean age at symptom onset (38.0 v. 44.2, p<0.05) and diagnosis (41.2 v. 47.1, p<0.05) was younger in PNES patients than PMD patients.

Conclusions: Patients with PNES and PMD have similarly low levels of quality of life, and high levels of somatization, depression, and anxiety. In addition, they have similar confidence in their ability to perform certain tasks or behaviors. There are differences in gender and age of onset and diagnosis in these groups. In addition, there is a difference in presentation of symptoms with PNES patients having more episodic symptoms. PNES and PMD patients are likely to represent the same patient population with regard to their psychosocial disorder. Their similarities in self-efficacy, which is a modifiable perception, may suggest that common treatment strategies and resources could be used for these patients. Collaborative efforts to investigate the management of PNES and PMD are warranted in the future.

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COMPARISON OF THE ASSESSMENT OF EFFORT IN PATIENTS WITH PSYCHOLOGICAL NON EPILEPTIC SEIZURES AND REFRACTORY PARTIAL EPILEPSY USING THE TEST OF MEMORY MALINGERING

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Rationale: The Test of Memory Malingering (TOMM) was originally developed as a symptom validity measure to assess effort and possible malingering of memory deficits, especially in litigating traumatic brain injury cases. Studies of patients with verified neurologic disorders such as dementia generally show that patients with substantiated poor memory "pass" this test. Patients with psychological non-epileptic seizures (PNES) have extensive cognitive complaints that are so profound as to sometimes appear exaggerated , but verification with symptom validity testing is rarely performed. The current study examines TOMM performance in an outpatient sample of adults with refractory partial epilepsy vs. PNES.

Methods: A retrospective chart review was performed to identify all patients who had taken the TOMM; this measure has been part of our standard neuropsychological battery since 2008. Forty-nine PNES patients and 31 epilepsy patients (consecutive with refractory partial epilepsy-taking 2 or more antoconvulsants) were included in the study. Neuropsychological testing was conducted on an outpatient or inpatient basis. Diagnosis of epilepsy vs. PNES was made by epileptologists following review of video-EEG monitoring. Independent t test was used for statistical comparison.

Results: Analysis of performance on Trial 1 of the TOMM revealed that 15 of 49 (31%) PNES patients failed trial one of the TOMM (mean score 42.6 +- 1.2) compared to 3 of 31 (< 10%) of the epilepsy patients (mean score 46.4 +- 0.8) (p<0.01). However, closer case review revealed that 6 of these persons had clear secondary gain associated to their symptoms (e.g. litigation following a motor vehicle accident, Worker's Compensation, and school avoidance). In another case, testing was discontinued due to significant fluctuation in arousal levels. When these patients were removed from the sample, the mean score was 44.8 +-1.0 and the difference between the groups was not significant (p<0.239).

Conclusions: Patients with PNES with no verifiable secondary gain do not differ significantly from an epilepsy sample.

Symptom validity testing is an important part of the standard PNES neuropsychological battery. Scores from these measures have the potential of providing important diagnostic information. These scores serve the purpose of alerting the clinician to possible secondary gain and may assist in the discrimination between conversion/somatization disorders (PNES) and malingering (NES).

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INTERICTAL DISCHARGES DURING ENCODING AND EFFECTS ON RECOGNITION

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Rationale: Prior studies found an association between disruptions of cognitive task performance and the presence of focal or generalized interictal epileptiform discharges (IEDs). Memory processes may be particularly vulnerable to IED effects. In an animal model, hippocampal spikes resulted in impaired spatial memory and object recognition compared to controls without epileptiform activity[1]. In humans, IEDs disrupted verbal and non-verbal short term[2] and long term[3,4] memory, and correlated with accelerated rates of long term forgetting[3]. We propose an effect of IED timing, in that IEDs during encoding will disrupt memory formation, leading to impaired recognition.

Methods: Subjects included adults diagnosed with temporal lobe epilepsy undergoing hippocampal depth, foramen ovale or subtemporal strip electrode placement for clinical purposes. During EEG recording, participants completed tests of verbal and non-verbal memory. In an encoding block, subjects were shown 50 stimuli (words or faces), presented one at a time on a computer screen. After a 5 minute delay with an intervening working memory (n-back) task, the subject's recognition of the stimulus items was tested. Recognition testing was administered in a two-choice format. IEDs were identified by manual review. Mixed model logistic regression was used to assess effects of the presence and laterality of IEDs during individual encoding trials on subsequent recognition of the stimuli.

Results: Seven subjects (2 female; 6 right-handed, 1 ambidextrous) of mean age 31 years (range 23-42 years) participated. Mean duration of epilepsy was 20 years (range 4-41 years). Seizures were of left-sided onset in 4 subjects, right-sided in 1 subject and bilateral in 2 subjects. No seizures occurred within 6 hours of testing. IED's were associated with very slightly higher error rates for faces (33% vs. 32%) and lower rates of errors for words (16% vs. 27%), however these differences were not statistically significant. No significant effect was evident for laterality of IEDs.

Conclusions: The present data demonstrated no significant relationship between the occurrence of IEDs during encoding of stimuli and later recognition of the stimulus items, nor any effect of IED laterality. This result may be contrasted with prior findings indicating a disruptive effect of IEDs on encoding[2]. It is possible that certain characteristics of IEDs are necessary for disruption to occur. These necessary features may relate to discharge duration, spatial extent,

timing relative to stimulus onset or presence of embedded high frequency components. It is also possible that the effect of IEDs depends upon the underlying functional and structural integrity of the hippocampus. This sample, with a long duration of epilepsy, may have impaired function of the hippocampus at baseline, such that the added disruptive effect of IEDs on encoding would be minimal. Further study of these variables in a larger sample will be necessary to determine in more detail the effects of IEDs on memory formation.

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NEUROPSYCHOLOGICAL OUTCOME FOLLOWING SELECTIVE AMYGDALO-HIPPOCAMPECTOMY

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Rationale: Selective amygdalohippocampectomy (SAH) is an accepted alternative for the surgical treatment of mesial temporal lobe epilepsy (MTLE). Reports suggest a potential cognitive benefit of SAH over standard temporal lobectomy. We present the cognitive outcome after SAH performed on a consecutive cohort of patients at the Calgary Epilepsy Program.

Methods: A retrospective analysis of all adult patients who underwent transcortical SAH using image and intraoperative MRI guidance was completed. Kaplan-Meier curve was plotted for seizure freedom. Pre- and post-operative cognitive performances (IQ, verbal and visual memory, working memory and language) were compared using reliable change index values.

Results: 83 patients were operated for SAH in the last ten years at the Foothills Medical Center. Complete pre- and post-operative neuropsychological evaluations were available for 53 patients (29 left side, 24 right side). Average age at surgery was 37 years (+/- 9). Seizure freedom was obtained in 65% of patients, and good outcome (Engel I or II) in 83%. There was no significant post-operative change in IQ or working memory. Visual memory (WMS III Delayed Visual Index) declined in 23% of patients operated on the right compared to 11% for left side operations. Verbal memory (WMS III Delayed Verbal Index) declined in 11% of patients operated on the left compared to 9% for right side operations. California Verbal Learning Test (CVLT) was more sensitive for detecting a post-operative verbal memory decline: 29% for left sided operations and 23% for right-sided. Naming (Boston Naming Test) deteriorated in 39% after left SAH compared to 4% after right operations.

Conclusions: Selective amygdalohippocampectomy is an effective treatment for the long-term control of intractable MTLE. Overall, memory changes were equivalent to or lower than rates reported for standard temporal lobectomy. However naming decline following SAH was similar to most series of standard temporal lobectomy. Because lateral neocortex is largely preserved in SAH, this may indicate an important role for mesial temporal structures in language. Alternatively, cortical disruption of the middle temporal gyrus may be resposible for naming changes after SAH

IMAGE: images/907236_A.jpg

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A NEW PERSPECTIVE IN THE ASSESSMENT OF THE PSYCHOLOGICAL COMPOSITION OF PATIENTS WITH PSYCHOLOGICAL NON-EPILEPTIC SEIZURE DISORDER

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Rationale: Significant advances have been made in the diagnosis of psychological non-epileptic seizures (PNES). However, knowledge about underlying psychological characteristics, and distinct sub-classifications is still limited. The Minnesota Multiphasic Personality Inventory (MMPI) has been the most utilized tool in the assessment of psychological structure: depression, hypochondriasis and hysteria scores form the classic triad in these patients. Since 2008, we added to our standard battery a set of measures that assess a supplementary series of psychological factors including anger expression, stress coping mechanisms, alexithymia, trauma symptomatology and quality of life.

Methods: Our standard battery for patients diagnosed with PNES includes the Trauma Symptom Inventory (TSI), Toronto Alexithymia Scale (TAS), State Trait Anger Expression Inventory (STAXI), Quality of Life in Epilepsy Inventory (QOLIE-31), Coping Inventory for Stressful Situations (CISS), Minnesota Multiphasic Personality Inventory-2 (MMPI-2) along with a comprehensive cognitive assessment. Diagnosis of PNES was made by epileptologists through review of video-EEG monitoring. Neuropsychological testing was conducted on an outpatient or inpatient basis on all patients who were referred.

Results: Sixty-four patients completed the PNES battery in its entirety or major portions of it. Seven were males and fifty-seven were females. Mean age was 35.7 years. Mean education was 13.7 years. More than half of patients carried a diagnosis of PNES for over 2 years. Forty (63%) were in mental health treatment and 39 (60%) were receiving psychiatric medication at the time the assessment was conducted. Twelve (19%) had suicide attempts and a psychiatric hospitalization in their past. Seventeen (27%) were employed although of those several were “underemployed” based on their educational attainment.

Clinically significant scores were defined as > 1.5 standard deviations from the mean. The following number of patients earned significant scores on the TSI scales: Anxious Arousal (18/42; 45%), Depression (16/42; 39%), Dissociation (15/42; 36.6%), Defensive Avoidance (15/42; 36.6%) and Intrusive Experiences (13/42; 31.20%). Alexithymia was endorsed by 17 out of 46 patients (37%). Fifteen of 47 patients (32%) reported that they tend not to address stressful situations using task-oriented strategies. Twenty-eight patients out of 50 (56%) reported clinically relevant scores on the total Anger Index of the STAXI. Seventeen of 33 patients reported impoverished overall quality of life.

Conclusions: These findings highlight discrete psychological factors in PNES patients that add to the clinical understanding provided by current standard psychological batteries. These factors are key in treatment planning and treatment target designation including anger

management, implementation of anxiety reduction techniques and treatment of the trauma triad (arousal, avoidance, intrusion).

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ANTEROGRADE MEMORY IN HUMANS IS RELATED TO DENTATE GYRUS GRANULE CELLS BUT NOT TO CA1 NEURONS

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Rationale: Hippocampal specimens obtained from mesial temporal lobe epilepsy (TLE, MTLE) surgery provide an excellent opportunity to study human memory-related pathology. Extensive preoperative memory assessments are available for correlation to histopathological analysis of resected hippocampi. IAT memory testing offers the unique possibility to access memory performance of each isolated hippocampus by intracarotid amobarbital anaesthesia. Additionally, verbal memory capacity could be related to the left hippocampus.

Methods: 1) In 24 patients with unilateral TLE declarative memory function were correlated to cell densities in the different hippocampal CA subfields and the dentate gyrus (DG), using IAT.

2) The neurogenic potential in the human DG could be investigated by isolating adult human neural stem cells from 23 surgical en bloc hippocampus resections.

3) In 75 unilateral TLE patients memory profiles were related to different patterns of neuronal cell loss in MTLE, i.e. to selective loss of CA1 pyramidal cells versus other MTS patterns.

Results: 1) Multiple regression and partial correlation analyses identified neuronal cell loss within the internal limb of the dentate gyrus, a developmentally distinct subregion of the hippocampal formation known to generate new neurons throughout life, as highly significant predictor for the patient's ability to learn and recall memories ($p<0.01$).

2) After proliferation of the progenitor cell pool in vitro two distinct patterns were identified: adult neural stem cells with a high proliferation capacity (HPC) were obtained in 11 patients, most of these cells were capable of neuronal differentiation. In 12 specimens a low proliferation capacity (LPC) were obtained with reduced numbers of proliferating cells in vivo. HPC and LPC groups differed considerably in declarative memory tasks, with normal memory performance in HPC and severe impairment in LPC ($r=0.813$; $p<0.001$).

3) Selective CA1 neuronal loss did not associate with memory deficits, either with IAT memory deficits, nor with verbal memory deficits compared to other MTS subtypes with cell loss in all hippocampal subfields and highly reduced memory capacities ($p< 0.001$ / ($p<0.05$).

Conclusions: The present results were compatible with animal studies, proposing that memory formation critically depends on the capability of the hippocampus to maintain and recruit new neurons into the dentate gyrus, and suggest a similar mechanism operating in humans. Our findings affirm that encoding new memories is related to the regenerative capacity of the hippocampus also in the human brain.

In contrast to the role of the DG, cell loss restricted to the CA1 subfield did not cause anterograde memory deficits as assessed by standard neuropsychological tests including IAT. This is in accordance with findings in experimental animal studies, suggesting that the CA1 region is implicated in long-term memory formation, but not in short-term memory acquisition or encoding.

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IMPAIRMENT OF PROSODY DURING EPILEPTIC SEIZURES CHARACTERIZED BY AUTOMATISMS WITH PRESERVED RESPONSIVENESS

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Rationale: Prosody describes the rhythm, stress, and intonation of speech and may be used to convey emphasis, emotions or commands. The loss of prosodial ability has been documented in stroke, but ictal epileptic changes of prosody have not been studied systematically. We aimed to evaluate the localizing significance of ictal changes of prosody in focal epilepsies. A prerequisite for this evaluation is preserved consciousness during epileptic seizures which is characteristic of seizures arising from the non-speech dominant hemisphere.

Methods: We compared ictal prosody by analyzing the speech frequency formants (frequency peaks) F1, F2, F3 and their energy as proxy for our analyses. We studied two groups of patients with epilepsy from our presurgical epilepsy monitoring unit. The first group comprised patients whose seizures were characterized by automatisms with preserved responsiveness (APR; n=29). This group had a predominantly right temporal seizure origin (15/29), four patients had a frontal lobe epilepsy and for seven patients the seizure onset could only be lateralized but not further localized to one lobe. The control group (n=14) was defined by ictal speech only and excluded patients eligible for the first group. Here the seizure origin was frontal or paracentral in nine patients, only one patient had a seizure onset in the left temporal lobe (1/14) and in four patients the exact region of seizure onset had not yet been determined. One seizure per patient was evaluated.

Results: Right-sided TLE was more common in the APR group (83%; 15/18) than extratemporal or hemispheric epilepsies (17%; 3/18; $p<0.001$). Quantitative speech analyses could be performed in 41% of the APR group (12/29) and in 71% (10/14) of the control group patients. It demonstrated a loss of prosodial ability in the APR group. The ictal frequency peaks were all of equal or lower frequency than interictally (F1: 169 ±131 Hz vs. 327 ±221 Hz, $p<0.01$; F2: 427 ±269 Hz vs. 428 ±301 Hz, not statistically significant; F3: 211 ±132 Hz vs. 297 ±157 Hz. $p<0.01$). In the control group no decrease or leveling of prosody in the frequency peaks was shown.

Conclusions: Ictal loss of motor prosody indicates seizure origin in the non-dominant temporal lobe. Therefore, this study demonstrates that prosody is a non-dominant temporal lobe function. This localizing information is particularly helpful in the evaluation of patients considered for resective epilepsy surgery.

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MESIAL TEMPORAL ACTIVATION ON MAGNETIC SOURCE IMAGING: RELATIONSHIP TO COGNITIVE TEST PERFORMANCE

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Rationale: Previously, we demonstrated possible relationships between Magnetic Source Imaging (MSI) mesial temporal (MT) activation using a word recognition paradigm, unilateral memory scores on the Wada test, and the presence of MT sclerosis. Greater activation of the right MT structures was more common in patients with left MTS and corresponded to relatively higher Wada memory scores following left injection. The question of whether MT activation represents memory processing per se vs. other types of cognitive functioning remains unresolved. In the present study, we re-examine MSI MT activation in relation to baseline neuropsychological test scores.

Methods: The subjects were 12 epilepsy or brain tumor surgery candidates who had undergone neuropsychological testing and who demonstrated MT activation in response to an auditory word recognition task during receptive language mapping with MSI. All patients had been classified left language dominant based on MSI criteria. The MEG unit consisted of a 148-channel Magnes 2500 WH system and data were analyzed using the single equivalent current dipole (ECD) model across each whole hemisphere. Patients were divided into left and right groups based on the hemisphere with the most MT activation. The two groups were compared on the following measures: Full Scale IQ, Boston Naming Test, Controlled Oral Word Association Test (COWAT), Animal Naming and the delayed recall score on the Verbal Selective Reminding Test (VSRT). The results were compared using the nonparametric Wilcoxen Mann-Whitney U sum of ranks test for small samples.

Results: Patients with more mesial temporal activation in the left hemisphere scored significantly higher on Full Scale IQ (mean = 107.4) and confrontation naming on the Boston Naming test (mean = 52) compared to patients with more activation in the right mesial temporal lobe (FSIQ = 92.7; BNT mean = 34.7). A similar trend was noted for the phonemic verbal fluency (COWAT) task but differences were not statistically significant. There was no difference between the two groups on the Animal Naming measure or delayed recall on the VSRT.

Conclusions: These limited results lend support to a cognitive interpretation of this MT activity that may extend beyond verbal memory. While performance on a delayed word recall task does not correspond to MT activation ipsilateral or contralateral to the language dominant hemisphere, a possible relationship to other word retrieval scores such as confrontation naming and phonemic verbal fluency is suggested. The explanation of increased MT activation in the right hemisphere of patients with clearly established left hemisphere dominance for language remains undetermined. However, these observations do suggest the need to examine in greater detail the inter-relationship of naming and verbal memory.

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TEST YOUR MEMORY: A SELF ADMINISTERED COGNITIVE TEST IDENTIFIES PEOPLE WITH JME WITH WIDE RANGING COGNITIVE DIFFICULTIES

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Rationale: Many features prevent juvenile myoclonic epilepsy (JME) from being defined as a benign epilepsy syndrome: in particular, although associated with normal IQ, people with JME identify complaints with memory. Detailed neuropsychometry is time consuming and costly if used indiscriminately. We set out to identify whether the self administered cognitive screening test - 'Test Your Memory' (TYM) designed as a screening tool for dementia - may help identify people with epilepsy with cognitive difficulties. The TYM tasks include orientation, verbal fluency, semantic knowledge, visuospatial abilities and calculation. A score of d"42/50 has a sensitivity of 93% and specificity of 86% in the diagnosis of Alzheimer's disease (Brown et al. BMJ 2009;338:b2030).

Methods: Nineteen people with a clinical and EEG diagnosis of JME attending detailed phenotyping interviews for genetic research, were asked to complete a TYM scale before attending their interview (seventeen remembered to do so). Participants also undertook a full Wechsler Adult Intelligence Scale (WAIS III), Wechsler Memory Scale (WMS III), three sub-tests of the Delis-Kaplan Executive Function System (D-KEFS), three sub-tests of the BADS (Behavioural Assessment of Dysexecutive Syndrome), and a semi-structured clinical interview. Results were analysed using the Student's t-test.

Results: Mean full scale IQ was 100 (SE +/-4) and the TYM scores ranged from 38 to 50 (mean score 46 (SE +/-1), median 48). A score of d"42/50 identified those people with the lowest full scale IQ scores ($p>0.0005$): all scoring d"42/50 struggled with naming and semantic knowledge tasks. Memory deficits and executive function difficulties were similarly identified by a TYM score of 42 or under, including: all WMS-III subscales ($p>0.001$); the FAS test ($p>0.0005$), inhibition on the D-KEFS colour word test ($p>0.03$), trail making task ($p>0.0006$) and elements of BADS - such as Key search ($p>0.0003$) and Zoo map ($p>0.02$). All of those with a score of d"42/50 in this study were in employment and only one had a pre-existing diagnosis of mild learning disability. There was no significant difference between those taking sodium valproate (n=9) and those who were not.

Conclusions: TYM is not specific for Alzheimer's dementia and may help identify people with epilepsy who have significant cognitive difficulties across a broad range of sub tests. JME may be more heterogeneous than previously thought, with certain subgroups demonstrating cognitive difficulties despite good seizure control. Low test scores across a range of scales may be due to attentional deficits. Educational achievement may also be lower due to delayed diagnosis and recurrent absence seizures during schooling (resulting in lower semantic knowledge scores). Because TYM tests a wide range of abilities including sequencing it is capable of identifying difficulties with concentration and attention. This freely available (www.tymtest.com) and patient friendly test may help clinicians identify people with idiopathic epilepsy who have significant cognitive difficulties.

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POSTOPERATIVE VERBAL MEMORY IN LEFT ANTERIOR TEMPORAL LOBECTOMY PATIENTS WITH BILATERAL AND RIGHT HEMISPHERE LANGUAGE REPRESENTATION ON THE INTRACAROTID AMOBARBITAL PROCEDURE

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Rationale: Individuals who undergo anterior temporal lobectomy in the left, language dominant hemisphere are at risk for postoperative verbal memory decline. It has recently been shown that the extent of language dominance in the left hemisphere can predict postoperative verbal memory outcome in these left language dominant ATL patients. Additionally, research has shown that left language dominant patients who undergo a non-dominant, right ATL are not at risk for postoperative verbal memory decline. However, studies of memory outcome in L-ATL patients with bilateral or right dominant language representation are more rare, and whether or not L-ATL patients remain at risk for verbal memory decline has not been conclusively determined. In the present study, we examined verbal memory outcome in L-ATL patients who had right dominant or bilateral language representation as determined by the Intracarotid Amobarbital Procedure (IAP).

Methods: Patients who met the following criteria of 1) bilateral or right language dominance as determined by a valid intracarotid sodium amytal test, 2) left anterior temporal lobe resection, and 3) valid pre and 1 year postoperative neuropsychological assessment with a verbal list learning test (12 trial Selective Reminding Test) were examined in the present study. A total of 12 patients were identified who met these criteria. Of these patients, 9 of 12 were right hemisphere dominant and 3 of the 12 were classified as bilateral according to the intracarotid amobarbital test. IAP methodology and classification criteria at our center have been previously published.

Results: A "significant decline" in verbal memory was determined as a greater than 2 standard deviation decline from pre to postoperative assessment on one or more subscales of the Selective Reminding Test. With this criteria, 5 of the 12 (42%) L-ATL patients with atypical language representation showed significant decline on one or more of the SRT scales. 4 of these patients (33%) were right hemisphere dominant for language as determined by the IAP.

Conclusions: While the number of patients with bilateral and right hemisphere language in the sample is small, there appears to be a risk for postoperative verbal memory decline after L-ATL with atypical language. Surprisingly, 4 of the 9 patients with right hemisphere language dominance showed a significant postoperative verbal memory decline after undergoing a supposedly "non-dominant" L-ATL. This is in contrast to individuals who are left language dominant who undergo a R-ATL, who are at minimal risk for verbal memory decline. Further studies of organization of atypical language representation in left and right ATL patients and its relationship to verbal memory outcome are needed not only from a scientific standpoint, but to aid in surgical planning in temporal lobe epilepsy patients.

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JUVENILE MYOCLONIC EPILEPSY: TWO DISTINCT PHENOTYPES CONSIDERING NEUROPSYCHOLOGICAL ASPECTS, PERSONALITY TRAITS AND CLINICAL VARIABLES

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Rationale: Studies demonstrate that patients with Juvenile Myoclonic Epilepsy (JME) have executive impairments. In addition, cluster B personality disorder has been reported in 20-30% when using the categorial classification of DSM-IV, corroborating the hypothesis of a frontal lobe deficit. To moment, there are no studies on personality traits as well as its correlation with executive dysfunction and clinical response to AED. This study aimed to: 1. verify executive/attentional déficits in patients with with JME with an extensive neuropsychological battery; 2. determine the severity of the attentional/ executive déficit; 3. verify personality traits with a valid instrument; 4. correlate performance on executive/attentional tests with expression of personality traits and clinical variables of epilepsy.

Methods: Forty-two patients with JME were evaluated by: i. comprehensive battery for executive and attentional functions; ii. Assesment of personality based on a questionnaire for evaluation of personality traits (TCI) and compared to 42 healthy controls, with no psychiatric and neurological diagnosis, matched by age, gender and social-economic status.

Results: Patients with JME had worse performance than controls on tests that evaluate immediate attention, mental control, selective and sustained attention, mental flexibility, inhibitory control, verbal fluency, concept formation, goal maintenance, and verbal short-term memory. Based on clinical criteria, 83,33% had severe to moderate executive dysfunction. Patients with JME presented higher expressions of impulsive personality traits compared to controls. Executive/attentional dysfunction was correlated with worse impulse control. There was a positive correlation between seizure frequency and the presence of psychiatric disorders, worse executive/attentional deficits and higher expression of impulsive traits. Longer duration of epilepsy and early age of onset were correlated with executive dysfunction and impulsive personality traits, respectively. The categorical analysis between groups of easy and hard to control-epilepsy showed that refractory patients had worse executive dysfunction and higher impulsive traits.

Conclusions: Our study demonstrates the presence of executive dysfunction and impulsive personality traits in patients with JME. In addition, we verified the existence of two distinctive groups of patients, being refractory JME patients were more globally impaired. These findings indicate the necessity of a better phenotypic characterization of patients with JME in order to include clinical endophenotypes.

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DECISION-MAKING IN MESIAL TEMPORAL LOBE EPILEPSY EXAMINED WITH THE IOWA GAMBLING TASK

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Rationale: Although memory, language, and executive functions have been extensively studied in patients with mesial temporal lobe epilepsy (MTLE), few investigations of the decision-making abilities of these patients have been performed.

Methods: We studied implicit decision-making (decisions under ambiguity) in right and left MTLE patients (n=20) using the Iowa Gambling Task. The Iowa Gambling Task is believed to detect deficits in decision-making caused by either ventromedial prefrontal cortex or amygdala lesions.

Results: In the present study, MTLE patients scored poorly compared to healthy controls on this task, and right MTLE patients exhibited worse performance than left MTLE patients.

Conclusions: Our findings indicate that the amygdalo-hippocampal complexes play important roles in decision-making. The right and left

amygdalo-hiippocampal complexes may play different roles in implicit decision-making in particular.

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ARE SOME OBJECTS IN WADA TESTING EASIER TO REMEMBER THAN OTHERS?

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Rationale: During the Wada procedure, memory tests are performed with a series of objects shown to a patient after sodium amobarbital is injected directly into the right or left internal carotid artery. When the drug wears off, the recall of those objects is tested. We explored if objects shown were distinctly more memorable than others.

Methods: 135 Consecutive adult Wada tests were performed from 1997-2004 in a standardized manner with sodium amobarbital injections into the right or left carotid artery with an 8 object memory exercise per side. After drug metabolism the 8 objects were tested for recognition intermixed with 16 different foil objects to test for false recognition (guessing). For study purposes, only first side injections were analyzed. At our center, all Wada tests start with amytal injections on the side of suspected disease burden. The majority of patients tested were undergoing surgical epilepsy work-ups. Item memory errors were compared between hemispheres via Chi square statistics by side of injection with two-tailed p tests and significance <0.05. No concession was made for side of language dominance.

Results: Irrespective of side injected, targets were correctly identified between 73-88% of the time. When left injections were done, right sided recalls showed clear and consistent trends for greater memory difficulties, with correct target identification medians of 77.5%. Conversely, testing recognitions with right sided injections, median correct identifications were 93%. Object recognition errors were apparent in all items, occuring more often when the left side was injected, and were most notable for the following 3 of 16 items: comb ($p=0.02$), frog and clothespin (both $p= 0.04$). False positive recognitions of foil items, although less common, showed similar errors with left sided injections, and of the 32 items, only the binder clip $p = 0.01$ and green dinosaur $p = 0.05$ were statistically notable.

Conclusions: Some objects shown during standardized Wada testing may be easier to recall than others, yet that effect is more notable when information is presented and encoded to the awake left hemisphere, where memory may be both visually and verbally encoded in the majority of patients.

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THE IMPORTANCE OF STUDYING SOCIAL ADJUSTMENT IN PATIENTS WITH TEMPORAL LOBE EPILEPSY: SUBJECTIVE PERCEPTION MAY NOT REFLECT THE REAL SOCIAL IMPACT OF EPILEPSY

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Rationale: Several studies have verified the negative impact of epilepsy on quality of life (QOL) in patients with temporal lobe epilepsy (TLE). However, measures of QOL evaluate only the patient's personal and subjective perceptions about the disease. Despite growing evidence on the occurrence of poor psychosocial adjustment, to moment there is no formal assessment of social adjustment (SA) using a validated instrument developed and standardized for this purpose. Our first aim was to assess the SA of patients with TLE compared to results obtained by QOL scales. Secondly, we verified the influence of cognitive performance and clinical variables of epilepsy on SA and QOL.

Methods: We evaluated 35 patients (15 men; mean 39.8 yrs (SD 9.0), with 9.1 yrs (SD 3.2) of schooling and an estimated IQ of 81.5 (SD 9.1)) compared to 38 controls (14 men; mean 28.6 yrs (SD 9.0) with 9.8 yrs (SD 2.3) of schooling and an estimated IQ of 94.2 (SD 8.0)). Assessment of QOL was done with Epilepsy Surgery Inventory-55 and Quality of Life in Epilepsy-31. Evaluation of SA was done with Social Adjustment Scale. All subjects underwent comprehensive neuropsychological evaluation and clinical variables of epilepsy were also considered. Statistical analysis was performed using SPSS software. The analysis of QOL was descriptive and in order to compare scores of SA, we used ANCOVA, controlled for age and estimated IQ. Neuropsychological performance was correlated with QOL and social adjustment with the correlation coefficient of Pearson or Spearman. This analysis was performed using Bonferroni correction ($p<0.000$). Analysis of the influence of clinical variables was performed using the Student t test or by analysis of variance.

Results: Patients showed worse SA factors in work, leisure and global SA compared to controls. In the descriptive analysis, the most affected domains of QOL were fear of seizures and cognition. We also observed strong and significant correlations between SA and the following tests: Verbal Fluency, Logical Memory I and II, RAVLT-total after interference and delayed recovery, and RVDLT-total after interference, delayed recovery and recognition. There was no correlation between QOL and neuropsychological performance. Regarding clinical variables, patients with left MTS had worse SA scores.

Conclusions: Social adjustment scale reflects more precisely the social insertion of patients with TLE than QOL questionnaires, since it objectively measures social adequacy of these patients in distinct domains. The lack of association between QOL and neuropsychological findings may indicate the imprecise nature of self-report scales. Clinical variables such as left TLE influenced SA, but not QOL, reinforcing the importance of distinguishing between these concepts. The association between social adjustment and cognitive performance emphasizes the importance of neuropsychological rehabilitation as part of the current concept of "treating beyond seizures".

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NEUROECONOMIC DICISION-MAKING IN PATIENTS WITH MESIAL TEMPORAL ROBE EPILEPSY BEFORE AND AFTER SURGERY

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Rationale: People do not always make rational decision People tend to overweight low probabilities and underweight high probabilities. For example, someone buys lottery tickets with low probabilities, and someone fears a plain crash than a car crush. This tendency is called "nonlinear probability weighting". And people tend to decrease the subjective value of reward in the future. For example, someone prefers to $90 available now than $100 available one month later. This is called "temporal discounting".

Peters and Buchel (2010) hypothesized that hippocampus codes temporal discounting and engages in episodic future thinking. We plan to confirm this hypothesis in patients with mesial temporal epilepsy, who are supposed to have hippocampal dysfunction.

Methods: The subjects were nine patients with mesial temporal lobe epilepsy who underwent unilateral hippocampectomy or hippocampal MST. The "probability weighting task" and "time-discounting task" was performed before and after surgery. In the "probability weighting", "probability weighting function" was evaluated. Two choices, one was a certain reward and the other was an uncertain and larger reward were presented, and the subjects were asked to select favorable one. In the "time-discounting task", "temporal discounting" was investigated. Two choices, one was a certain reward and the other was a delayed and larger reward were presented, and the subjects were asked to select favorable one. The informed consents were taken from all the subjects.

Results: In the probability weighting task, patients showed a pronounced tendency to overweight low probabilities and to underweight high probabilities after surgery compared with before surgery. In the time-discounting task, patients showed a higher temporal discounting tendency after surgery.

Conclusions: The patients tended to show more irrational decision-making after surgery in probability weighting task. It may be suggested that hippocampectomy changes the probability weighting function and increases gambling tendency. The patients also tended to show more pronounced time-discounting after surgery. It may reflect increased impulsiveness. Considering with the previous study, hippocampectomy might affect adversely to the function of episodic future thinking.

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NEUROANATOMICAL CORRELATES OF LINGUISTIC PROCESSES THAT COMPRISE NAMING: IMPLICATIONS FOR NAMING DIFFICULTY IN LEFT TLE

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Rationale: Cortical language mapping involves the identification of essential language cortex, which is typically spared from resection with the goal of preserving postoperative language function. Object naming is the most widely used task for this purpose; however, when stimulation impedes naming, it is unclear whether this reflects impaired access to word meaning (i.e., semantics), word sound (i.e., phonology), or both. This distinction is clinically relevant, with implications for level of disability and amenability to remediation. Two sets of psycholinguistic tasks were administered at sites where stimulation impaired naming to determine whether semantic vs. phonological processes were disrupted. Access to distinct types of word information is critical in the two tasks: information about word meaning in the semantic task, information about word sounds in the phonological task. We hypothesized that semantic and phonological naming sites would be anatomically distinct.

Methods: Subjects were 12 pharmacologically intractable, TLE patients (9 female, mean age = 34.8, SD = 11.1) who underwent extraoperative language mapping prior to surgical resection for seizure control. Stimulation mapping tasks included visual object naming and auditory description naming. At sites positive for naming, two psycholinguistic tasks were administered: 1) Semantic task: patients were presented pictured items during stimulation and indicated (via "button press") whether the item belongs to a particular semantic category (e.g., edible, found indoors); 2) Phonological task: patients indicated whether the item name begins with a particular sound (e.g., "p" or "f").

Results: Across patients, we identified 53 naming sites (38 visual naming, 15 auditory naming). Semantic task performance was impaired at 3 of these sites, phonological task performance was impaired at 14 of these sites, and both semantic and phonological task performance were impaired at 7 of these sites. Topographically, phonological-naming sites were broadly distributed across left lateral temporal cortex, whereas semantic and mixed semantic-phonological naming sites were found primarily in the posterior and inferior left temporal region. There was no clear pattern evident in phonological versus semantic processing related to auditory versus visual naming sites.

Conclusions: Results suggest that naming impairment related to anterior temporal abnormalities is due primarily to impaired phonological processing, whereas naming impairment resulting from posterior or inferior temporal damage reflects problems with both semantic and phonological processing. As the anterior temporal region is typically most affected in TLE, we speculate that naming difficulty in left TLE primarily reflects problems accessing information regarding word form, with relatively preserved access to word meaning.

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INDUCTION OF PSYCHOGENIC NON-EPILEPTIC EVENTS: SUCCESS RATES VARY WITH ICTAL SEMIOLOGY AND NEUROPSYCHOLOGICAL PROFILE

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Rationale: Psychogenic non-epileptic events (PNEE) represent paroxysmal behaviors that are caused by heterogeneous psychopathological processes rather than epileptic neuronal discharges. Three major groups of PNEE based on ictal semiology are hypermotor, hypomotor and experiential groups. Several investigators have supported the use of induction techniques for provocation of habitual PNEE of relevance, reporting success rates in the range of 77 to 84%. We hypothesize that the success rate of induction varies with ictal semiology of the presenting event of interest. Secondly, we hypothesize that neuropsychological profiles and/or demographic factors may influence the success rate of induction.

Methods: We enrolled veterans admitted to the epilepsy monitoring unit at the Michael E. DeBakey VA Medical Center from December 2008 until April 2010. Patients with epilepsy or mixed disorder of epilepsy and PNEE were excluded. According to the routine protocol at this center, provocative techniques such as photic stimulation, hyperventilation, and placebo injection are used for induction of events of interest in patients without a spontaneous event during the first 48 hours. The events of interest were categorized into three groups based on the semiologic features mentioned above. Most of the patients also completed 4 neuropsychological questionnaires: Dissociative Expressive Scale (DES), Structured Inventory of Malingered Symptomatology (SIMS), Test of Memory Malingering (TOMM), and brief COPE inventory.

Results: Demographic data of the 51 patients who were included in the analysis and their final categorization based on semiology of their event of interest is shown in the table. 24 out of 26 (92.3%) patients in the hypermotor category had successful induction of their habitual event of interest, leading to definitive diagnoses of PNEE. On the other hand, only 13 out of 20 (65%) patients in the hypomotor category had successful induction (p=0.029) (figure). Due to the small number of patients in the experiential group (n=5), the inductive success rate in this group could not be confidently assessed. Demographic and neuropsychological data were compared between the successful induction and unsuccessful induction groups. The main significant difference was the higher percentage of patients who had a SIMS score of more than 14 in the successful induction group compared to the unsuccessful induction group (p=0.035).

Conclusions: We observed that induction techniques were statistically more likely to provoke hypermotor PNEE as compared to hypomotor PNEE (p = 0.029). It can be possible that our hypomotor cases represented a wider spectrum of etiologies, including epileptic, physiologic non-epileptic, feigned, or other events not typically known to demonstrate suggestibility. Such etiologic diversity may in part explain the diminished induction success rate for hypomotor events. We observed a significant association of elevated SIMS score (> 14) among successfully induced cases, which may support the tendency toward over-reporting or exaggeration of symptoms among inducible patients.

Table - Demographic data of study subjects

IMAGE: tables/881313_T1.jpg

* Comparing hypermotor and hypomotor groups only

IMAGE: images/881313_A.jpg

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CORRELATION BETWEEN PSYCHOLOGICAL NON EPILEPTIC SEIZURE SEVERITY AND SELF REPORTED STATE/TRAIT ANGER AND ANGER EXPRESSION

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Rationale: From a psychodynamic perspective, psychological non epileptic seizures (PNES), especially those that have a very violent and extreme motoric output, can be conceptualized as expressions of repressed anger and frustration. As such, an inverse correlation between conscious assertiveness and endorsed trait/state anger and severity of behavioral expressions during PNES seizures could be expected.

Methods: Thirty five patients who underwent video-EEG monitoring and were diagnosed with PNES were administered the State Trait Anger Expression Inventory-Second Edition (STAXI-2) as part of their standard neuropsychological battery. The Staxi-2 is a 57-item inventory that measures anger as an emotion state, the disposition to an angry trait, and an index of anger control/expression. All patients were studied in order to determine whether there was a correlation between their state, trait and expression scores and the behavioral severity of their seizure-like events. Subjects with mixed PNES and epileptic seizures, or physiological NES were excluded. A PNES behavioral severity scale was used to rate the intensity of the patients' episodes on a scale of 0-5. This scale was developed using a previous study which objectively classified PNES by cluster analysis of semiologic features into 3 categories of severity (Gröppel et al.). Episodes were scored using these criteria: decreased responsiveness (Y=1, N=0), maximal motor activity (no movement=0, trembling=1, clonic/hypermotor=2), head movement (Y=1,N=0), and pelvic thrusting (Y=1,N=0). An epileptologist reviewed at least 3 videos for each subject and selected the most habitual event for scoring.

Results: No significant correlations were noted in any of the STAXI-2 subscales. Spearman's rank correlation coefficient was calculated between the behavioral severity scale and the STAXI-2 variables. The correlation between the overall Index score and severity was not significant (r=-.60, p<.734). Correlations were also non-significant between the behavioral severity score and Anger State (r=.02, p<.928) and Anger Trait (r=-.07, p<.676).

Conclusions: There was no significant correlation between the PNES behavioral severity scale and the overall anger index, state and trait as measured by the STAXI-2. This suggests that conscious endorsement of anger expression in situations of intense fury and angry state/trait characteristics do not correlate with seizure semiology in this population. Possibly, one of the greatest weaknesses in this design is the fact that the study is relying on self-report of an emotion that is so central in this disorder characterized by dissociation and denial. Therefore, another way to obtain anger assessments might be obtained through objective observer rating scales of assertiveness and anger expression.

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A COMPARISON OF SELF-REPORTED QUALITY OF LIFE IN MEDICALLY REFRACTORY PARTIAL EPILEPSY PATIENTS AND PSYCHOLOGICAL NON EPILEPTIC PATIENTS

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Rationale: For epileptologists, establishing a strong patient-doctor working alliance with the psychological non epileptic patient (PNES) can be problematic since the disorder is not neurological. The fact that the lives of many PNES patients appear more disrupted than some very compromised epilepsy patients can also be striking from a medical perspective. However, these groups share a number of similarities. As in epilepsy, patients with PNES can experience many of the same concrete limitations (e.g. driving prohibition, the need for work and school accommodations) and secondary impacts of seizures (e.g. the unexpected nature of seizures, injuries as a result of seizures, stigma). Co-morbidity with depression and anxiety is also common. The purpose of this study was to determine whether diminished quality of life (QOL) in PNES is comparable to that reported by medically refractory epilepsy patients.

Methods: Twenty seven consecutive patients with refractory partial epilepsy (uncontrolled seizures and taking 2 or more anti epileptic drugs at the time of the assessment) and 33 patients with PNES (diagnosed by an epileptologist through video-EEG monitoring) who completed the QOLIE-31 test were included. Where necessary, the word "epilepsy" was replaced with "seizures" in the PNES inventory. Cognitive, emotional, energy, medication effects, overall, seizure worry, social function and total scores (components of the QOLIE-31) were compared between groups using independent t test.

Results: For the epilepsy group and PNES groups, mean age was 41 years and 38 years respectively. Gender distribution was 4 males and 29 females in the PNES group and 11 males and 16 females in the epilepsy group. Mean years of education was 14 years for the PNES group and 12.66 for the epilepsy group.

Epilepsy and PNES scores were the following: mean Cognitive scores (48.7 +- 3.0 vs 38.5 +- 1.8), Emotional scores (39.07+_2.18 vs 31.1 + -1.38), Energy/Fatigue scores (50.52+-2.9 vs 38.18+-1.9), Medication Effect scores (46.37+-3.3 vs 45.82+_2.0), Overall QOL (51.53+_3.20 vs 39.64+-2.1), Seizure Worry (51.26+-3.1 vs 31.91+-2.2), Social functioning (42.78+-3.4 vs 38.82+-2.2), and Total score (44.90+-2.6 vs 33.79+-1.7).

PNES patients reported significantly worse QOL in the following areas: Cognitive functions ($p < 0.006$), Emotional ($p < 0.002$), Energy/Fatigue ($p < 0.001$), Overall QOL ($p < 0.004$), Seizure Worry ($p < 0.003$), and Total score ($p < 0.001$).

Conclusions: Patients with PNES reported diminished QOL and in fact, significantly lower total QOL, energy, and cognitive functions and significantly greater worry about seizures than patients with refractory partial epilepsy. This reveals that the emotional distress and effect that this disorder has on these patients is experienced as profound.

Regardless of the neurological or psychological etiology of the disorders, both epilepsy and PNES patients report significantly diminished quality of life. Results from this study underscore the importance of compassionate care and timely/appropriate referrals for PNES patients.

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PSYCHOSOCIAL FUNCTIONING IN EARLY- AND LATE-ONSET INTRACTABLE COMPLEX PARTIAL SEIZURES

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Rationale: Individuals with epilepsy have greater complaints of psychosocial functioning including educational and vocational difficulties. Early-onset of seizures can potentially affect cognitive development as well as disrupt school and work routines. We hypothesized early-onset would create greater psychosocial difficulties in adulthood because of risk of greater cognitive disability and disruption of school/work routine due to seizures from an earlier age.

Methods: Participants were consecutive adult epilepsy patients with intractable complex partial seizures. To reduce the noise on cognitive data created by different epilepsy types, participants were limited to unilateral temporal lobe focus (n=47). Early seizure onset was defined as at or before the age of 5 years (n=15) and late-onset was defined as older than 5 (n=32). There were no significant differences in gender, age at evaluation, or side of seizure focus between the early- and late-onset groups. The participants underwent a comprehensive neuropsychological evaluation as part of a presurgical assessment. Neuropsychological variables considered in this study include IQ as determined by Wechsler Adult Intelligence Scale-III (WAIS-III), Boston Naming Test (BNT), and Washington Psychosocial Inventory (WPSI).

Results: WAIS-III IQ in the early-onset group (M=84.7) compared to the late-onset group (M=93.2) was borderline worse ($F=3.84$, $p=.056$). Naming ability(BNT) in the early-onset group (M=43.7) compared to late-onset group (M=50.7) was significantly worse ($F=8.55$, $p<.01$). Educational attainment in early-onset (M=12.7) and late-onset (M=13.2) were comparable ($F=.58$, $p=.45$). Both the early- and late-onset groups reported elevated complaints on the WPSI Vocational Adjustment, Financial Status, Emotional Adjustment, and Overall Psychosocial Functioning scales. However, there was no significant difference between the early- and late-onset groups on those scales.

Conclusions: These findings suggest that an epilepsy diagnosis rather than age of seizure onset or specific cognitive deficits affects psychosocial functioning including educational attainment, vocational adjustment, and emotional distress. Individuals with early-onset seizures may have been able to recruit more coping resources from their environment to compensate for earlier disability such as special education services in school etc. It is also possible that the early-onset group has become inured to their disabilities, and is reporting fewer psychosocial difficulties in adulthood. This was a retrospective study; ideally, a prospective longitudinal study would be useful in understanding the psychosocial sequelae of early-onset seizures.

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MEMORY PERFORMANCES OF RIGHT AND LEFT TEMPORAL LOBE EPILEPSY PATIENTS ON THE WMS-IV, RAVLT, AND ROCFT

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Rationale: Pre-surgical neuropsychological assessment of temporal lobe epilepsy (TLE) patients can be informative and guide clinical decision-making because of the increased risk of memory and language impairment after left temporal lobe resections. One of the most popular and well-studied memory measures, the Wechsler Memory Scale (WMS), has recently been revised (i.e., Wechsler Memory Scale - Fourth Edition; WMS-IV). While the WMS-IV may be used to assess pre-surgical lateralization of function, its clinical utility and incremental validity have been questioned. We analyzed the WMS-IV as well as more commonly used cognitive measures, the Rey Auditory Verbal Learning Test (RAVLT) and Rey-Osterrieth Complex Figure Test (ROCFT), to assess lateralization differences in memory between left and right TLE patients.

Methods: Neuropsychological testing was administered to pre-surgical TLE candidates. Participants: A total of 25 participants met criteria for this study which included EEG and MRI evidence of seizure focus. There were 11 left TLE (LTLE) and 14 right TLE (RTLE) patients. Variables/Measures: Participants completed comprehensive neuropsychological evaluations which included the WMS-IV, RAVLT and RCOFT.

Results: Intelligence, education, and age did not differ between LTLE and RTLE groups. ANOVA found that WMS-IV primary indices (Auditory Memory, Visual Memory, Immediate Memory, and Delayed Memory) were similar for each group. In contrast, a subtest analyses found that LTLE patients performed significantly worse than RTLE

patients on the Logical Memory I (p=0.030) and Logical Memory II (p=0.034) subtests, which are immediate and delayed measures of prose memory. LTLE patients also performed significantly worse than RTLE patients on the Immediate Recall (p=.036), Delayed Recall (p=0.042), and Recognition (p=0.041) trials of a list-learning measure (RAVLT). During the recognition task, LTLE patients also made significantly more false positive (p=0.23) and false negative (p=0.006) errors. No significant lateralizing differences were found on a test of visual memory (ROCFT).

Conclusions: These data suggest that the WMS-IV and ROCFT have limited clinical utility when differentiating between left and right TLE dysfunction in pre-surgical candidates. In contrast, the Logical Memory subtests of the WMS-IV were sensitive to laterality of the seizure focus. As found in previous research, several scores from the RAVLT demonstrated clear clinical utility and sensitive to left temporal dysfunction. While the changes in the updated WMS-IV have promise to better lateralize right TLE dysfunction, these data failed to support such a claim. Future investigations should be pursued in order to assess the validity of WMS-IV for pre-surgical TLE patients.

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PREDICTORS OF DECLINE IN VERBAL FLUENCY AFTER FRONTAL LOBE EPILEPSY SURGERY

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Rationale: Cognitive outcomes after temporal lobectomy for treatment of intractable epilepsy are well characterized in the literature. However, despite being the second most common type of partial epilepsy, outcomes after frontal resection are not well known. This study examined changes in verbal fluency in patients who underwent surgery for frontal lobe epilepsy (FLE).

Methods: A retrospective chart review of patients who underwent epilepsy surgery at the Cleveland Clinic from 1991 through 2008 was performed. Inclusion criteria were: aged 18 or older, diagnosis of frontal lobe epilepsy, completed pre and postoperative neuropsychological testing that included phonemic verbal fluency, and available postoperative MRI. Patients with prior epilepsy surgeries were excluded. Resection site and extent was characterized using imaging software (MRICro) to identify the involvement of the following regions: superior medial frontal (SMF), inferior medial frontal (IMF), orbitofrontal (OF), and lateral frontal (LF) lobe (with or without Brodmann area 44). Patients were categorized into two groups based on postoperative change in their verbal fluency scores using standardized regression based change scores (i.e., decline n=10 and no decline n=27). A series of logistic regression analyses were then conducted to identify predictors of decline in verbal fluency.

Results: 37 patients were identified who met inclusion criteria (19 right FLE; 18 left FLE), 41% were female. Average age was 30.24 ± 10.58 years. Preoperative seizure frequency was 54.4 seizures per month, and 68% were seizure-free at the time of postoperative neuropsychological testing. There were no significant differences between the two study groups in age, education, age at seizure onset, duration of epilepsy, Full Scale IQ, or preoperative verbal fluency performance. Patients without verbal fluency declines were more likely to be seizure free after surgery, and there was a trend for them to have a longer test-retest interval as compared to the decline group. Preoperative imaging showed MRI abnormalities in 62% and PET abnormalities in 89%. The area of resection included: SMF (95%), IMF (66%), OF (50%), LF with Brodmann 44 (18%), and LF without Brodmann 44 (63%). Logistic regression using relaxed input criteria (p = .1 to add to model, p = .15 to remove from model) indicated both lesion location (p = .051) and preop FAS score (p = .112) are predictive of verbal fluency decline (R2 = .155; p = .052). These two variables accurately predicted decline in 71% of patients. As noted, patients who declined on verbal fluency were also less likely to be seizure free after surgery.

Conclusions: Twenty seven percent of patients who underwent FLE surgery showed a decline in verbal fluency. This decline did not appear to be due to general intellectual decline or post-operative aphasia. Preoperative predictors of decline include a high pre-surgical verbal fluency score and a left lateral frontal lobe resection (with sparing of Broca's area). Cognitive deficits can be noted postoperatively even if patients have resections of the "non-eloquent" cortex.

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NONEPILEPTIC SEIZURES, EPILEPTIC SEIZURES, AND INTRASUBTEST SCATTER

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Rationale: Nonepileptic seizures (NES) resemble epileptic seizures but are typically identified by a lack of epileptogenic activity on EEG studies. While the use of EEG studies remains the gold standard in separating such patients from those with epileptic seizures, patients in question are often also administered a battery of neuropsychological tests and questionnaires to provide further substantiation of their apparent psychological etiology. Proper diagnosis is important, as presentation of diagnostic findings may lead to cessation of or a decrease in seizure activity. The aim of this study is to explore the potential utility of another possible marker of nonepileptogenic seizures - amount of intrasubtest scatter on subtests of intelligence testing. In this case, it was suggested that patients with a history of seizure activity would demonstrate significantly greater amounts of scatter than those with suspected nonepileptic seizures. That is, it was suggested that organic factors would play a larger role than nonorganic factors in producing intrasubtest scatter.

Methods: A total of 26 cases were included in the study, 13 presurgical cases with a documented history of epileptogenic activity on EEG studies and 13 nonepileptic seizure cases with a documented history of no epileptogenic activity on EEG studies. The mean ages of the two samples were 43.69 and 42.46, and the mean education levels were 13.46 and 13.00, with no significant differences between the groups. All of the cases had previously completed a neuropsychological battery, including administration of the Wechsler Abbreviated Scale of Intelligence. There were no significant differences between the two groups for the WASI IQ indices or subtest raw or scaled scores. Amount of scatter was calculated for each of the four subtests for each patient. Differences in mean amounts of intrasubtest scatter on the four subtests between the two groups were examined using a MANOVA approach.

Results: No significant differences were found between the two groups on the four WASI subtests using six different approaches for calculating intrasubtest scatter.

Conclusions: Analyses demonstrated no significant differences for amounts of intrasubtest scatter. Further research with intrasubtest scatter with larger samples may produce different results. These findings initially suggest little utility for employing intrasubtest scatter in distinguishing between those with epileptic seizures and those with nonepileptic seizures. This is consistent with research demonstrating

no differences between the two groups on measures of intelligence or neuropsychological testing. However, the results also reinforce the suggestion that a given diagnosis should not be made on the basis of one clinical factor but rather a combination of factors. Furthermore, neuropsychological testing, and intrasubtest scatter in particular, remain important aspects of a patient's evaluation for documenting current levels of cognitive functioning (as well as variability within such) as markers for possible treatment, depending on the severity and persistence of such.

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PERCEIVED MEMORY IMPAIRMENT BEFORE SURGERY IN TEMPORAL LOBE EPILEPSY

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Rationale: Patients with temporal lobe epilepsy (TLE) often complain of memory impairment. Objective measures of memory function do not always reflect the degree and severity of subjective memory complaints.

Methods: We used a validated 10 item Frequency of Forgetting scale (FOF10) to assess subjective memory in 55 preoperative patients with TLE compared to 76 controls without epilepsy. Results were analyzed in comparison to age, gender, laterality of seizure focus, neuropsychological test results, depression (CES-D) and neuroticism (PANAS).

Results: Mean age was 39 years (42% males) for patients and 42 years (50% males) for controls. The mean score for the FOF10 in patients was 43.9 and in controls 51.8 ($p<0.001$, lower score indicates perceived poorer memory). FOF10 scores did not correlate with age, gender or laterality of seizure focus. Neuropsychological test results were consistent with memory impairment in 61% of TLE patients but the findings did not correlate with the FOF10 results. Correlation of the FOF10 score with depression(CES-D, $p=0.04$) and neuroticism(PANAS, $p=0.07$) approached significance.

Conclusions: Perception of memory impairment in presurgical patients with TLE is greater than in controls. This may relate more to emotional factors than to defective memory mechanisms in the temporal lobe.

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EPILEPSY AND CREATIVITY, INSIGHTS FROM THE CREATIVE LIFE AND WORK OF CANADIAN PLAYWRIGHT JUDITH THOMPSON

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Rationale: The relationship between epilepsy and creativity has been the subject of much speculation. For example, it has been suggested that temporal lobe epilepsy enhanced the creativity of artists such as Dostoyevsky, Lewis Caroll, Vincent Van Gogh, and Michelangelo leading to paradigm shifts in arts and literature. Objectively the effect of TLE or epilepsy surgery on creativity has been difficult to study because creativity is not well suited to study through psychological methods based on the observation of group performance over multiple trials in stereotyped circumstance. Here we examine the relationship between temporal lobe epilepsy (TLE) and creativity in the autobiographical and theatrical work of Canadian playwright laureate Judith Thompson.

Methods: Literature review of biographic and autobiographic material on writers with epilepsy is used to contextualize our analysis of Thompson's autobiographical writing and her play about two women with epilepsy, The Perfect Pie (TPP).

Results: In her autobiographical writing Thompson makes a direct link between her ictal experience and her creative process. She describes both as a descent into chaos and self-loss, one involuntary and the other voluntary. In her writing process, identity, specifically fully rendered character, emerges through this frightening descent. In part, the experience of TLE, allows the playwright to shed herself in order to embody her characters. She likens the fear of death associated with her seizures to her fear of self-loss through her sometimes harrowing creative process. TPP offers a unique dialogue woven of the voices of three women with epilepsy - the playwright, and her two characters - Marie and Patsy. Marie begins as a young girl from the wrong side of the tracks with post-traumatic epilepsy. Her epilepsy remits as she sheds her small town roots to become an actress. Yet she must reclaim her past and her epilepsy to become whole. Patsy begins as a relatively privileged girl in a cruel and close-minded small town. She 'contracts' epilepsy through her encounter with Marie. In her case, her epilepsy signifies the empathy and humanity that distinguishes her from the others around her who victimize Marie. Thus, a re-interpretation of the stereotype of epilepsy as stain or contagion lies at the play's core. Epilepsy is not exoticized. Seizures occur on stage and the social consequences are explored. At the same time epilepsy is also a symbol of personal transformation through an expansion of empathy and consciousness. For the characters, as for the playwright, integrity arises from the descent.

Conclusions: The Perfect Pie is a landmark portrayal of epilepsy in modern theatre. Thompson's portrayal of epilepsy in tandem with her reflections upon her own epilepsy are rich in metaphor yet provide concrete insight into the subjective, social, and creative aspects of epilepsy. In the absence of validated paradigms for assessment of creativity in patients with TLE, the study of autobiographic and creative work of artists with epilepsy is a valuable source of insight for physicians.

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INADEQUATE UTILITY OF A CLINICAL METHOD FOR PREDICTING THE ULTIMATE SIDE OF SURGERY IN PATIENTS WITH TEMPORAL LOBE EPILEPSY USING THE BOSTON NAMING TEST

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Rationale: One of the major contributions of neuropsychological assessment in the preoperative setting is to assist in the lateralization of the seizure focus. The Boston Naming Test (BNT) is sensitive in respect to the side of seizure focus with the worst scores indicating seizure origin in the speech dominant temporal lobe. Busch et al. (Epilepsia 2009; 34(6):1270-1273) provided a method that may help to lateralize seizure focus using the Boston Naming Test while controlling for duration of epilepsy, onset, and intelligence. This study aims to test the clinical utility of this method in predicting the ultimate side of surgery using a sample of 34 patients with temporal lobe epilepsy (TLE).

Methods: Patients (n=34; left TLE=18; right TLE=16) ranged in age from 18-59 (M=39.12; SD=12.31) and in education from 8-17 years. The study group was equivalent to the Busch et al., (2009) combined group in terms of intelligence, age at onset, duration of epilepsy, and BNT score. The method provided by Busch et al., in addition to alternative prediction models based on logistic regressions, was used to predict ultimate side of surgery.

Results: Applying the equation introduced by Busch et al., it was possible to correctly predict the side of surgery in 61.8% of patients (Chi-Square=3.031; p=.087). A more parsimonious model using BNT as the sole predictor correctly predicted 73.5% of patients (Chi-Square=8.476; p=.004).

Conclusions: The usage of the regression equation provided by Busch et al. resulted in an unsatisfactory prediction of the ultimate side of surgery in patients with medically intractable TLE. Improved prediction was possible after specifying model coefficients based on our own sample. However, a less complex model with the Boston Naming Test as the only predictor resulted in an equally good prediction. The failure of the proposed prediction method may have resulted from overfitting, caused by an excessively complex model. According to the principle of parsimony models with the fewest number of parameters are most preferable.

Prediction of the ultimate side of surgery

IMAGE: tables/905645_T1.jpg

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PRE-SURGICAL WECHSLER ADULT INTELLIGENCE SCALE - 4TH ED. FUNCTIONING AMONG SELECTED RIGHT AND LEFT TEMPORAL LOBE EPILEPSY PATIENTS

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Rationale: Epilepsy is a common neurological disorder with cognitive and psychiatric comorbidity. About 30-40% of patients with complex partial epilepsy have seizures that are refractory to medication. These patients are candidates for neurosurgical treatment, commonly a temporal lobectomy. Patients with temporal lobe epilepsy (TLE) can exhibit deficits in intellectual functioning, and the presence of cognitive deficits have implications for surgical outcome. The WAIS-IV is the most recent version of a commonly used measure of intellectual function. However, little data are available regarding the performance of patients with known neurological disease on the WAIS-IV (Bauer and Loring, 2010). The current study compares the pre-surgical performance of patients with left TLE (LTLE) to patients with right TLE (RTLE) across the WAIS-IV index and subtest scores

Methods: The study included review of epilepsy patients completing a pre-surgical evaluation for medically refractory epilepsy. Participants: Twenty five patients were identified that met study inclusion and exclusion criteria. There were 11 participants diagnosed with left TLE and 14 individuals with right TLE. Variables/Measure(s). All participants completed comprehensive neuropsychological assessment as part of a Phase I presurgical evaluation.

Results: The Left TLE group mean age was 36 years (SD = 15.9) and had 12.9 years of education. The mean age of right TLE group was 31 years (SD = 15.9) and had 13.5 years of education. The average FSIQ, VCI, PRI, and PSI indices of the left TLE group significantly differed from the population parameter of 100 (Left TLE, FSIQ = 87.8, VCI=91.0, PRI=89.5, WMI=90.9, PSI=88.7). the average FSIQ, VCI, and PRI index scores of the right TLE group significantly differed from the population parameter of 100 (RTLE; FSIQ=88.4, VCI=88.8, PRI=91.3, WMI=93.3, PSI=93.5). ANOVA revealed no significant differences in presurgical WAIS-IV index or subtest scores between the left and right TLE patients (p>.05).

Conclusions: As expected, patients with right and left TLE performed below the average population parameter on the measures of general cognitive, general verbal and general nonverbal abilities (p<.05). The LTLE group also scored significantly below average on a measure of processing speed. However, there was no significant difference between patients with LTLE versus those with RTLE. These data are consistent with past studies using previous versions of the Wechsler Adult Intelligence Scales which demonstrated the WAIS does not reliably lateralize patients with known left or right TLE. Implications for surgical treatment and cognitive outcome are discussed.

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VAGAL NERVE STIMULATOR : COGNITIVE AND MOOD ASPECTS

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Rationale: Vagal Nerve Stimulator insertion is indicated for drug-resistant epilepsy patients, who did not qualify for resective surgery. Literature reports positive reactions on seizures, mood, cognitive functions and Quality of Life after Vagal Nerve Stimulator procedure.

The aim of our study is to evaluate neuropsychological functioning, Quality of Life and mood conditions pre and post (one year follow-up) Vagal Nerve Stimulator insertion, in order to verify the influence of this procedure on cognitive and mood variables.

Methods: The inclusion criteria are: consecutive patients, treated at the Epilepsy Center, Neurology 2, S. Paolo Hospital, University of Milan, not qualified for epilepsy surgery, with a drug-resistant epilepsy, aged 18 or more.

A complete neuropsychological battery has been administered to all 14 selected patients. This battery includes tests for the assessment of intelligence level, attention, short term verbal memory, short term visual memory, long term verbal memory, long term visual memory, language, a questionnaire on mood status and another one on Quality of Life. All these instruments are validated in Italy.

Results: The first one-year follow-up highlights an improvement of Quality of Life and mood conditions. The cognitive functions seem stable.

Conclusions: Our first data are encouraging; we believe that it is important to enlarge our sample, in order to have more reliable results.

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AGE-RELATED VULNERABILITY TO RISKS FOR NEUROPSYCHOLOGICAL DECLINE FOLLOWING SEIZURE ONSET IN SCHOOL-AGE CHILDREN

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Rationale: We prospectively examined changes in neuropsychological functioning for 36 months following seizure onset in children and examined the degree to which risk factors for deficits and decline varied with age of onset.

Methods: We followed 228 children ages 6-14 years who had experienced a first recognized seizure and 125 sibling controls; the two groups did not differ on age or sex. Seizure control, AED use, and syndrome were obtained by chart review and interviews with parents at baseline, 9, 18, 27, and 36 months. Seizure control was classified at 36 months into 3 groups: Single-Seizure (n=56; only 1 seizure), Recurrent (n=143; 2+ seizures but not at every clinical follow-up), Persistent (n=29; seizures at every follow-up). AED use was classified at 36 months into 3 groups: Never (n=62; no AED at any time), Partial (n=61; AED at one or more 9-month follow-ups but not all follow-ups), Continuous (n=105; AEDs at all follow-ups). Neuropsychological testing at baseline (M=2.8 months after first seizure) and at 18 & 36 months after onset yielded 4 age-corrected factors: Language, Verbal Memory & Learning, Processing Speed, Attention/Executive/Construction skills (higher scores are better). Epileptic syndrome was defined by ILAE criteria. Mixed models were used to investigate change in factor scores over time by age and by risk factors (AED use, seizure control, epileptic syndrome). Hochberg's step-up Bonferroni method was used to adjust for multiple comparisons.

Results: There was an Age x Time x Seizure Control interaction on Processing Speed ($p=0.0006$); poor seizure control increased the risk of decline in processing speed over time, but only in younger children (Figure 1). In addition, there were Age x Seizure Control interactions on Attention/Executive/Construction ($p<0.0001$) and on Verbal Memory & Learning ($p=0.04$), with younger age of onset amplifying the risk associated with poor seizure control in both domains across the 3-year study period. There was an Age x AED interaction on Verbal Memory & Learning ($p=0.02$); in the older and middle age ranges, the Continuous AED Group had lower memory scores vs. Siblings and vs. the Partial-AED Group; however, in the youngest age range, no AED groups differed significantly (Figure 2). There were no interactions between age and epileptic syndrome.

Conclusions: Younger age of seizure onset was clearly associated with increased vulnerability to the effects of undercontrolled seizures on neuropsychological functioning. Unexpectedly, older children seemed to be more vulnerable to adverse cognitive effects of AEDs; this could reflect differences in AEDs used (oxcarbazepine more common in younger vs. older; valproate more common in older vs. younger), but this study was not a randomized controlled trial, did not measure blood levels, and included heterogeneous syndromes; also, AEDs might have different adverse effect profiles at different ages. Thus, seizure control is critical to cognitive development in younger school-age children; the impact of AEDs warrants further examination. Funded by NIH/NINDS R01 NS22416 (Austin)

IMAGE: images/901115_A.jpg

Figure 1. Relationship Between Seizure Control and Processing Speed for Children with Earlier Onset, From Baseline (B) to 18 months (M18) to 36 months (M36).

IMAGE: images/901115_B.jpg

Figure 2. Relationship Between AED Use and Verbal Memory, by Age of Onset (Years).

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THE EFFECT OF DEVELOPMENTAL AND ACQUIRED BRAIN LESIONS ON HEMISPHERE LANGUAGE DOMINANCE IN CHILDREN

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Rationale: Children with epilepsy have a higher incidence of atypical language dominance. Factors that have been associated with atypical language dominance in children include left handedness, focal seizures arising from the left hemisphere and lesions of the left hemisphere. The objective of this study was to identify the effect of acquired and developmental brain lesions on language dominance in children.

Methods: This a retrospective cohort study of 64 children with MRI documented brain lesions who underwent presurgical fMRI for language lateralization from January 2005 - December 2008 at the Hospital for Sick Children in Toronto, Canada. Routine presurgical 1.5 tesla MRI scanning was performed to investigate for structural abnormalities, and reported by a pediatric neuroradiologist. Lesion type was classified as developmental (eg. brain malformation, cortical dysplasia) or acquired (eg. stroke, tumor). Blood oxygen level dependent fMRI for language lateralization was performed at 1.5 tesla, utilizing a minimum of 2 standardized language paradigms. Studies were analyzed using AFNI and visually inspected and rated for lateralization and localization of frontal and temporal lobe language areas. Atypical language dominance was defined as right or bilateral hemisphere dominance for frontal and/or temporal language areas.

Results: Children with acquired lesions were more likely to demonstrate atypical language. Sixteen of 32 (50%) children with acquired lesions demonstrated atypical language in contrast to 9 of 32 (28%) of children with developmental lesions. Lesion location also had an effect on language dominance. Nine of 22 (41%) of children with left temporal lesions demonstrated atypical language in contrast to 3 of 16 (19%) of children with right temporal lesions ($p<0.05$). Furthermore, for lesions of the left temporal lobe, 8 of 14 (57%) children with acquired lesions demonstrated atypical language in contrast to 1 of 8 (13%) children with developmental lesions ($p<0.05$). This is also true for left frontal lesions, with 3 of 4 (75%) children with acquired lesions demonstrating atypical language in contrast to 3 of 8 (38%)with developmental lesions.

Conclusions: Children with acquired brain lesions are more likely than children with developmental lesions to demonstrate right hemisphere or bilateral language dominance on fMRI. In this cohort of 64 children, only 28% of those with developmental lesions demonstrated atypical

language dominance. This is true even of children with left hemisphere developmental lesions, with only 26% demonstrating atypical language. This is of critical importance in the planning of neurosurgical and epilepsy surgery procedures in children. It cannot be presumed that the critical language centres in children with left developmental lesions will undergo inter-hemispheric reorganization.

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MOTIVATIONAL EFFECTS ON EXECUTIVE FUNCTION IN PEDIATRIC EPILEPSY: AN FMRI AND DTI STUDY

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Rationale: Pediatric epilepsy is associated with compromised quality of life due to behavioral limitations including executive function and motivation. We probed the integrity of the neural systems underlying executive function and reward processing in pediatric epilepsy.

Methods: Seventeen non-lesional, medically treated pediatric epilepsy patients 8-17 years of age (mean age 13 years, mean duration of epilepsy 3 years) and individually age and gender-matched healthy community controls completed whole brain functional MRI (fMRI). During fMRI subjects performed a monetary incentive-mediated antisaccade task of response inhibition using an event related design. A cue preceding antisaccade trials indicated if subjects could win points towards a monetary reward or if the trial did not involve a monetary incentive (neutral). Participants completed 4 fMRI runs and activation from correct trials was analyzed for group differences using multivariate analyses. Diffusion tensor imaging (DTI, 6 diffusion gradient orientations with 14 sequential averages, b0=800 s/mm2) scanning was completed by a similar group of 27 epilepsy patients (mean age 13 years, mean duration of epilepsy 3 years) and 88 age approximated controls at 3T. DTI analysis used tract based spatial statistics to localize regions of compromised white matter (lower fractional anisotropy) in patients compared to controls.

Results: In the fMRI task, both groups demonstrated improved inhibitory control during reward vs. neutral conditions. However, patients made more inhibitory errors compared to controls. A widely distributed region known to support inhibitory oculomotor control and reward processing was similarly evident in both groups including visual cortex, superior parietal cortex, and orbital frontal cortex. However, patients demonstrated significantly less activation in the middle frontal gyrus, a putative cognitive control region. Higher activation in the middle frontal gyrus was associated with better antisaccade performance in the control group. DTI results showed broadly distributed regions of lower fractional anisotropy in association tracts (uncinate, superior longitudinal fasciculus), projection tracts (anterior thalamic radiations, internal capsule, and cortical spinal tract), and interhemispheric tracts (anterior and posterior corpus callosum) in the patients compared to controls. Patients had lower fractional anisotropy in the internal capsule, an important prefrontal-striatal connection in association with lower fMRI activation in the middle frontal gyrus compared to the controls.

Conclusions: Pediatric epilepsy is associated with poorer inhibitory control. While motivational effects may improve cognitive performance, patients demonstrate persistent cognitive limitations which may be associated with poorer prefrontal cortex recruitment and compromised white matter integrity in prefrontal-striatal tracts. Structural and functional brain correlates of cognitive comorbidity may have long term implications for developmental outcome in pediatric epilepsy.

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CLINICAL CHARACTERISTICS OF PSYCHOGENIC NON-EPILEPTIC SEIZURES (PNES) IN CHILDREN

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Rationale: Studies of adults report certain clinical characteristics of seizures such as eye closure, side-to-side or alternate limb movements, hyperventilating, crying, etc. suggest a higher probability of psychologically based nonepileptic seizures. However, there is very little literature on the clinical characteristics of psychogenic non-epileptic seizures in children. We have described the clinical characteristics of PNES in children compared to those reported in the adult literature.

Methods: Following IRB approval, chart audit was performed to identify children given the diagnosis of PNES by video-EEG and psychological evaluation. Children 13 y.o. or younger were included in the study if a complete video-EEG of their events had been obtained during the inpatient epilepsy unit evaluation. Video-EEGs of the events were reviewed for 23 separate features attributed to PNES in adults.

Results: There were 20 children, 12 female, 8 male, mean age 11.45 years (range 8 - 13). 36 events were evaluated. All 20 had at least 1 event with unresponsiveness. Sixty percent (12) of children had 4 or more characteristics to suggest PNES. In this group, 60% had gradual onset of arrhythmic jerking, 50% had side-to-side movements, 45% seizures with eyes closed, 40% out-of-phase extremity movement, 35% had large variability in seizure expression from one event to the next one, 30% at least one seizure over 2 minutes, and 10% had pelvic thrusting or crying. Only 1 patient had events with no features typical of PNES, 3 other patients had only 1 feature.

Conclusions: PNES in children may share some of the clinical characteristics seen in adults. When the more common clinical features of PNES in adults are reported or observed in children, it should raise ones awareness to the possibility that the events actually may be PNES.

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SYSTEMATIC REVIEW AND CASE SERIES OF NEUROPSYCHOLOGICAL OUTCOMES AFTER EPILEPSY SURGERY IN CHILDREN WITH DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOURS (DNET)

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Rationale: There is dearth of literature examining neuropsychological (NP) outcomes in children with DNET. Aims were to 1) conduct a systematic literature review of NP outcomes after epilepsy surgery for DNET, and 2) present NP results from a case series of children with DNET using reliable change methodology.

Methods: A systematic review of all studies on DNET that included neuropsychological (NP) or cognitive outcomes was conducted. The case series involved a retrospective review of surgical patients seen at Alberta Children's Hospital with DNET diagnoses confirmed by pathology. The NP assessment included measures of intellectual functioning (IQ), visual-spatial abilities, verbal and visual memory, and questionnaires examining executive and adaptive functioning, attention, and quality of life (QOL). Reliable change indexes and qualitative methods were used to examine post-surgical NP changes in functioning.

Results: Of 50 studies including DNET cases, only 7 studies included information on cognitive outcomes in children. No studies included a comprehensive evaluation of NP functioning. Overall, studies reported low average to average IQ in children with DNET. Engel Class I seizure outcome was approximately 85%. Few cognitive changes were reported post-surgery, aside from some improvements in psychological functioning. Case Series: A retrospective review identified 7 children (3 boys, 4 girls) with DNET, ranging from 3.7-16.4 (mean = 11.27) years of age at the pre-surgical NP evaluation. Mean age at seizure onset was 10.19 years. The duration of epilepsy was less than 1 year in five children, and greater than 2 years in two children. Complex partial seizures were most common and seizure frequency was approximately 6 seizures/week. Time to post-surgical follow-up ranged from 0.7-2.7 years. At follow-up, 6/7 children were seizure free and 2 children were no longer taking antiepileptic medication. Their full-scale IQ ranged from 56-99 pre-surgically (average=85.86) to 75-108 post-surgically (average=89). Pre-surgically, children demonstrated low average to average functioning on most NP measures, but attention and executive functioning problems were prevalent in 3-4 of the cases. Post-surgically, there was little change in functioning with the exception of two cases. One child suffered a stroke post-surgically and demonstrated reliable declines in 7/9 NP tests. Another child who had English as his second language demonstrated post-surgical reliable improvements on 6/9 NP tests. The remaining 5 children demonstrated little reliable change post-surgically. Qualitatively, executive functioning, adaptive functioning, and QOL improved in over half of children.

Conclusions: Findings from this systematic review and small case series indicate that children with DNET demonstrate largely average NP functioning pre-surgically and few declines after surgery. Improvements in executive skills, adaptive functioning and QOL are reported in a substantial proportion of children after surgery.

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SUBJECTIVE VERSUS OBJECTIVE MEMORY IN PEDIATRIC EPILEPSY: CAREGIVERS' MEMORY RATINGS REFLECT OBJECTIVE MEMORY PERFORMANCE BETTER THAN SELF-RATINGS

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Rationale: The relationship between subjective memory complaints and objective memory performance has been explored in a number of adult populations, including patients with epilepsy. Results suggest that subjective memory is often more related to mood than to actual memory performance. While there is much data documenting memory deficits in children with epilepsy using standardized tests, there is little research examining subjective memory complaints. The few studies that have been conducted suggest that, similar to findings in adults, children's subjective memory relates more to mood than to objective memory performance. The current study was designed to: 1) replicate prior research examining the relationship between subjective and objective memory in children with epilepsy and 2) extend prior research by examining the relationship between caregivers' ratings of their child's memory and the child's objective memory performance.

Methods: As part of a neuropsychological battery, thirty-six pediatric patients (male=20; mean age=10.50, SD=2.59) with epilepsy (focal=24; generalized=12) completed a objective measure of memory [Children's Memory Scale (CMS)] as well as self-report measures of memory [Child Memory Scale (srCMS)], depression [Children's Depression Inventory (CDI)], and anxiety [Revised Children's Manifest Anxiety Scale (RCMAS-2)]. Mean age at seizure onset was 6.01 years (SD=3.02) and mean duration of epilepsy was 4.43 years (SD=2.93). Average Full Scale IQ was 82.19 (SD=13.80) and mean education level was 5.05 years (SD=2.73). Caregivers also completed a questionnaire exploring child's memory [Child Memory Scale Parent Form (CMSPF)]. The CMSPF consists of a total score, a Prospective Memory Factor (PM), and a Learning and Retrieval Factor (LR).

Results: Bivariate Pearson correlations revealed that children's subjective memory complaints related to depression ($r=-.458$, $p<.05$) and anxiety ($r=-.577$, $p<.01$), but not to objective memory performances (r range =.037 to .363). In contrast, caregiver reports of child's memory were significantly related to objective memory performance. Specifically, the LR factor of the CMSPF significantly correlated with the verbal memory indices of the CMS ($r=.423$ to .544, $p<.01$) and the CMS General Memory Index ($r=.507$, $p<.01$), but not the visual index scores ($r=.174$ to .326). The total CMSPF score significantly correlated with the CMS General Memory Index ($r=.359$, $p<.05$). PM did not significantly correlate with any CMS indices ($r=.056$ to .294). Interestingly, the CMSPF was not significantly related to srCMS ($r=-.045$ to .114), CDI ($r=.002$ to .137) or RCMAS ($r=-.088$ to -.152).

Conclusions: Consistent with the limited pediatric literature, self-reported memory in children with epilepsy is more related to mood and anxiety than to actual memory ability. Expanding on previous research, this study found that caregivers' report of child's memory ability more accurately reflects performance on objective memory tests than child's self-report of memory.

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ARE COMORBIDITIES IN PEDIATRIC EPILEPSY FAMILIAL?

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Rationale: The neurobehavioral comorbidities of pediatric epilepsy (psychopathology, impaired cognition, linguistic deficits, and abnormal brain volumes) are inconsistently related to seizure variables. Since psychiatric disorders, intelligence, language, social communication, and brain structure are heritable, it is important to determine if the comorbidities of these children reflect familial effects. From the psychosocial perspective, however, having a sibling with epilepsy could also contribute to psychiatric and poor academic achievement in the sibling without epilepsy. We, therefore, compared psychopathology, IQ, language, social communication, and fronto-temporal volumes in the siblings of children with epilepsy (Epi-S) to those of their epilepsy probands (Epi-P) and to healthy control subjects (Ctl-P) and their siblings (Ctl-S). Within the Epi-S group, we also examined the association of Epi-P illness variables with Epi-S psychopathology and academic achievement.

Methods: The study included 288 children (49 Epi-S, 85 Epi-P, 61 Ctl-P, 33 Ctl-S) with 46 Epi-S/P and 30 Ctl-S/P pairs, aged 6-17 years. Structured psychiatric interviews, IQ, language, social communication, and academic achievement testing were administered to all subjects. Parent and child self-report questionnaires provided information on behavior problems, depression, and anxiety. Children underwent MRI scans at 1.5 T. Tissue was segmented and total brain, frontal lobe, frontal parcellations and temporal lobe volumes were computed. Parents and medical charts provided epilepsy-related information. Mixed models controlling for age, gender, socioeconomic status and ethnicity were estimated on psychopathology, IQ, language, social communication, and volume measures in the study groups, using family as a random effect. Posthoc analyses compared Epi-S with Ctl-P and Epi-P groups. Within Epi-S, regressions were used to see if psychopathology and academic achievement were associated with proband seizure frequency and age of onset.

Results: The Epi-S and Ctl-P groups did not differ significantly on most of the measures except number of children with mean Full Scale (20% vs. 7%, $p<.04$) scores one standard deviation below average, parent report of more school problems ($t(67)=2.75$, $p<.008$), and trend for higher psychiatric diagnosis rate (31% vs. 14%, $p<.06$). The Epi-S differed significantly from Epi-P on all measures except psychiatric diagnosis rate (31% vs. 44%, $p>.2$). Epi-P older age of epilepsy onset was related to Epi-S psychopathology ($X2(1)=4.0$, $p<.05$) and poor academic achievement ($t(42)=2.7$-2.3, $p<.01$-$.03$).

Conclusions: The increased rate of cognitive deficits, school problems, and psychiatric diagnoses in Epi-S imply a familial effect not found for language and brain volumes. However, our findings underscore the need to also examine potential psychosocial effects, such as how later onset of epilepsy affects the emotional well-being and school performance of siblings of children with epilepsy.

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PEER ACCEPTANCE AND FRIENDSHIPS IN CHILDREN WITH EPILEPSY

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Rationale: Children with epilepsy experience greater social isolation and have more difficulties with peers compared to healthy controls and to children with non-neurologic disease. Children's relationships with their peers are associated with multiple aspects of development and adjustment and thus play an important role in long-term psychosocial functioning. We therefore assessed peer relationships in children with epilepsy as reported by their classroom peers, who are involved in social interactions with them on a daily basis over time.

Methods: Twenty-eight children with established epilepsy ages 9-11 years were asked to participate. The twenty-six schools (93%) of these 3rd to 6th grade subjects agreed to participate in the project. The children spent at least 50% of their time within the regular classroom setting. Friendship nominations and the peer acceptance ratings were collected in the classrooms of these schools. A classmate control was obtained for each child with epilepsy at the time of the classroom data collection, by identifying a participating classmate matched for gender, race, and age. During friendship nominations children are asked to write the names of the 3 peers in their class whom they think of as best friends. Children received scores based on the number of times they are chosen as friends by classmates. In addition, a reciprocal friendship score is generated based on the number of times children receive friendship nominations from classmates they also picked as friends. During the peer acceptance rating scale children are asked to rate all of their classmates on a five-point scale ranging from "someone you do not like" to "someone you like a lot". An average acceptance score is computed for each child based on the ratings from classmates. Scores for children and their classmates controls were compared using the Mann-Whitney test.

Results: Children with epilepsy were significantly less likely to be identified as a best friend by their classmates compared to their classroom controls ($p=0.04$). They were also less likely to be chosen as reciprocal best friends compared to their classroom controls ($p=0.03$). However, classmates did not rate children with epilepsy differently from classmate controls on the peer acceptance rating scale ($p = 0.28$).

Conclusions: This first study using information obtained through friendship nominations and peer acceptance ratings provided by classmates, demonstrates that peers prefer not to seek out friendships with children with epilepsy. In other words, perceived friendships of children with epilepsy are not reciprocated. This finding is of concern given the important role that friends play in children's social development. Our results set the groundwork for future studies that focus on better understanding peer relationships in children with epilepsy.

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GENDER DIFFERENCES ON MEMORY PERFORMANCE IN CHILDREN WITH LEFT TLE

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Rationale: A number of studies have suggested that females have a relative advantage for verbal memory as compared to males in normal populations, although this finding has not been universal. This has also been demonstrated in several studies of adults with temporal lobe epilepsy. A recent report sought to determine if this finding also extends to children with intractable epilepsy. Boys and girls were compared on their performance across several memory measures including delayed story recall, immediate and delayed word-list learning, delayed complex design recall, and delayed face recognition (Smith ML, Elliott I, & Naguiat A, 2009). These authors found that girls demonstrated an advantage over boys on delayed recall of stories and on the learning phase of the word list. No other memory differences were observed between the groups. The current study sought to replicate this research in an independent sample of children with left temporal lobe epilepsy.

Methods: 22 children (10 boys, 12 girls) who were candidates for left temporal lobe resection underwent neuropsychological evaluation prior to undergoing epilepsy surgery. Children ranged in age from 6 to 15 years (mean=11.14 (2.9)) The groups were not different in terms of age, age at seizure onset or duration of epilepsy. The Girls group was slightly older than the Boys group (avg. 11.75 vs. 10.4), but not significantly so. Memory performance of Boys and Girls was compared using select subtests from the Children's Memory Scale (i.e., story memory, word pair learning, spatial learning, and facial recognition). FSIQ for the Girls group was higher and had a medium effect size ($d=.58$). Given the relatively small sample size in each of the two groups, effect sizes (Cohen d) were used to examine group differences rather than relying on traditional significance testing (i.e., p values). Moderate to large effect sizes (i.e., .5 and higher) were considered meaningful.

Results: Girls demonstrated better memory performance than Boys on all delayed memory measures (d range = .57 to .71) with the exception of facial recognition (d range = .19 to .48). Girls also demonstrated superior immediate recall of stories (d = .628) as compared to Boys. No other significant differences were observed between the groups on immediate memory tasks (d range =.129 to .312).

Conclusions: Consistent with the findings of Smith et al. (2009), girls in the current study obtained higher scores than boys on a delayed story recall measure and did not demonstrate any significant differences in delayed facial recognition. The current study extends those findings by demonstrating differences in memory performance on measures of word pair recall and delayed recall of spatial locations in a sample of children with intractable left temporal lobe epilepsy. The reason for the observed sex differences is unclear, but may be a reflection of a difference in neurocognitive plasticity proposed by Trenerry et al (1995). Future research will seek to determine whether these differences are also observed post-operatively, and whether sex confers differential risk for memory outcome following temporal lobe resection.

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RETENTION SCORE AS A METRIC OF MESIAL TEMPORAL DYSFUNCTION IN PEDIATRIC EPILEPSY

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Rationale: While memory impairments are frequently reported in association with chronic epilepsy, especially when associated with temporal lobe foci, the vast majority of studies have used global memory measures based on normative comparisons. In contrast, relatively few have evaluated specific memory components as they relate to anatomical regions of epileptogenic activity, particularly in children. The present study compared verbal memory performance between epilepsy cases involving pathology in the neocortex, mesiotemporal region, and dual pathology involving both areas. Specific metrics of word list learning and memory were statistically evaluated to determine the best clinical index of hippocampal dysfunction.

Methods: 73 subjects 5-22 years of age (mean age=13.05) were given comprehensive neuropsychological testing prior to epilepsy surgery. Participants were 54% male, and 88% right-handed. Histopathologically, 43 were classified as having focal cortical dysplasia (FCD), a developmental aberration of the neocortex, 15 had hippocampal sclerosis (HS), and 15 had dual pathology consisting of both HS and FCD. For all hippocampal involvement, 18 were left lateralized, with 12 on the right. Assessment included the Word List subtest of the Wide Range Assessment of Memory and Learning (WRAML). Scores were evaluated for their ability to predict dysfunction of mesial temporal memory systems based upon known histopathological findings.

Results: There were no differences between those with and without hippocampal involvement for delayed memory (p=.23) or total list learning (p=.56). However, mean retention [delayed recall raw score / last learning trial] was statistically lower for those patients with HS than those without (p=.04). In contrast, difference scores [last learning trial-delayed recall score] reflected no contrast (p= .33) between groups. Data for memory recognition were not available for analysis.

Conclusions: The data suggest that for word list memory, retention score may be the best indicator of hippocampal involvement. Owing to the complexity of memory processing, networks are vulnerable to disruption at multiple locations, and diminished memory performance does not in and of itself suggest mesial temporal dysfunction. The retention score is a metric of information storage across time, and is less influenced by executive and other processes than are normative scores. Although "difference scores" are used in some memory tests to compensate for initial memory recall, they may be biased by the magnitude of constituent scores; as noted in this study, difference scores did not correlate well with hippocampal pathology. Statistical power was limited by a small sample, as mesial temporal sclerosis is not frequently seen in young populations. Further study is warranted to replicate findings and determine how lesion location (temporal vs. frontal), lesion laterality, and age of seizure onset affect various aspects of memory performance with use of a retention score.

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IS THE WISC-IV USEFUL FOR DETECTING COGNITIVE IMPAIRMENT IN CHILDREN WITH EPILEPSY?

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Rationale: The Wechsler Intelligence Scale for Children - 4th Edition (WISC-IV) sees widespread use in children with epilepsy. However, despite numerous studies on IQ in childhood epilepsy, most used previous editions of the test and none provide information on the sensitivity of specific WISC scores (FSIQ, index and subtest scores) to epilepsy-related cognitive impairment. The goal of this study was to determine WISC-IV index and subscale strengths and weaknesses in children with epilepsy and define the relationship between WISC-IV scales, demographic factors and epilepsy variables.

Methods: Retrospective data from clinically-referred children between ages 6 and 16 were recruited at the Alberta Children's Hospital and the New York University Comprehensive Epilepsy Center. All received a neuropsychological assessment that included the WISC-IV.

Results: WISC-IV scores were available for 106 children (46 girls, 60 boys; mean age = 11.0, SD = 3.1) with mean maternal education of 14.6 years (SD = 3.04). Of the sample, 69.4% were Caucasian, 76% were right handed, 54% had a positive MRI, and 44 had a clearly lateralized focus on EEG involving either the right (18) or left hemisphere (26). Most had early-onset epilepsy, were on multiple AEDs, and had high seizure burden. There were no significant differences between sites on demographic, epilepsy variables or FSIQ. The mean FSIQ was low average (M = 80.07, SD = 22.60) as were the means for the WISC-IV index scores, and 35.8% of children had FSIQ < 70. Mean Verbal Comprehension Index (VCI) was significantly lower than Perceptual Reasoning Index (PSI; p = .01), and PRI was greater than Working Memory Index (WMI) and Processing Speed Index (PSI; p = .01, p < .0001, p < .0001, respectively). No other differences between index scores were found. At the subtest level, mean scores were highest on the Matrix Reasoning (M = 8.12, SD = 3.73) and lowest on Coding (M = 5.87, SD = 3.60). In terms of percent of children on each subtest with low scores (i.e., scores below 2SDs from the expected normative mean of 10), Coding identified the most children (28.3%) with low scores, and Similarities identified the fewest (11.3%). Later age at onset and shorter epilepsy duration were both correlated with higher WISC-IV FSIQ and index scores (rs ranging from .36 to .45, p <.0001), and number of current and previous AEDs were inversely correlated with FSIQ and index scores (rs = -.25 to -.46, all ps < .0001). Neither the FSIQ or index scores were related to seizure frequency. A similar pattern was found for subtest scores. No differences in FSIQ, index

scores or subtest scores were found between children with left and right seizure foci, or between MRI-positive and MRI-negative children.

Conclusions: The WISC-IV is sensitive to epilepsy-related cognitive impairment in children, particularly those relating to expressive verbal, working memory and processing speed. Although WISC-IV scores are related to markers of epilepsy severity such as age at onset, the test should not be used for inferring seizure laterality.

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USE OF SPECIAL EDUCATION SERVICES IN CHILDHOOD-ONSET EPILEPSY:A CASE-SIBLING-CONTROLLED ANALYSIS

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Rationale: Children with epilepsy have an increased burden of cognitive, behavioral, and psychiatric disorders and have poorer school achievement and performance even when their epilepsy is of presumed genetic or unknown etiology (i.e. absence of mental retardation, normal neurological exam, no underlying structural or metabolic neurological condition or insult).Special education is a crude marker for a heterogeneous group of disorders that can interfere with school performance.The purpose of this study was to assess if the use of special education services was associated with epilepsy among cases of presumed genetic or unknown etiology.

Methods: Data came from the Connecticut Study of Epilepsy of 613 children with newly diagnosed epilepsy (cases) prospectively identified by pediatric neurologists from 1993 to 1997.Our analysis is based on a parent interview conducted 8-9 years after each child was first diagnosed with epilepsy.Sibling controls were recruited in order to control for social environment, parent education, school district, access to educational diagnoses, medical care, and sensitivity of physicians diagnoses.We restricted the analysis to 217 cases of presumed genetic or unknown etiology and their 217 sibling controls.Cases and sibling controls were compared using the Chi-squared test or the Fisher's exact test, and logistic regression.

Results: Mean age at the time of the interview was 15.3 for cases (SD 4) and 15.7 for controls (SD 5).Based upon parent report, cases were more likely than the sibling controls to have ever repeated a grade (OR=2.1, 95% CI=1.2-3.6) and ever received special education services (OR=4.0, 95% CI=2.6-6.2).Among those who ever repeated a grade, 31 (73.81%) cases and 14 (63.64%) controls were held back between kinder-garden and second grade.Among cases who had ever received services, for 32 (29.09%) services were initiated before their first seizure.This was true for 7 (12.73%) cases with an age of onset <5 years, 19 (44.19%) if age of onset 5-9 years, and 6 (50%) if age of onset >10 years.Among cases, the odds of ever receiving one special education service was three-fold higher than the controls (95% CI =1.7-5.3) and the odds of ever receiving two or more special education services was five-fold higher than the controls (95% CI=2.8-7.8).Cases were also more likely still to be receiving services at the nine-year interview compared to controls (OR=3.4,95% CI=1.7-6.9).

Conclusions: Our analysis suggests that the use of special education services is associated with childhood-onset epilepsy even if the children appear neurologically otherwise normal.Many services were initiated before epilepsy onset, and more services were provided to children with epilepsy than to their siblings.These findings suggest that even in children with presumed genetic or unknown etiology, subtle deficits exist.Medical providers who care for children with newly diagnosed seizures should be responsive to the special educational needs of such children not only at the time of diagnosis but over their school years as well. Funded by: NIH-NINDS R37-NS31146.

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CLINICAL NORMATIVE DATA FOR INTELLIGENCE TESTING IN CHILDREN AND ADOLESCENTS WITH EPILEPSY

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Rationale: It is well known that epilepsy has a negative impact on a child's intellectual development. Cormack and colleagues (2007) reported that intractable epilepsy can result in at least a 1-2 standard deviation difference in mean intelligence compared to healthy children. Although determining strengths and weaknesses in relation to healthy peers is important, it is also valuable for clinicians to be able to determine whether a child's cognitive abilities are similar to, above, or below the level expected for patients with refractory epilepsy. The purpose of this study is to present clinical normative data for WISC-IV performance in American and Canadian patients with refractory epilepsy.

Methods: Participants included consecutively referred children and adolescents between the ages of 6-16 years with medically-determined refractory epilepsy from the New York Comprehensive Epilepsy Centre (American sample, n=50) and the Calgary Epilepsy Programme in Calgary, Canada (Canadian sample, n=76). All participants were administered the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003) as part of their clinical work-up.

Results: American participants had a mean age of epilepsy onset of 4.9 years (SD=4.3; range=0-14.3 years), mean duration of epilepsy of 6.0 years (SD=4.0; range=0.1-15.4 years), and a mean number of previous antiepileptic medications of 2.1 (SD=2.1; range=0-10). The mean age at assessment for the American sample was 10.9 years (SD=3.3; range=6.5-16.3 years). Canadian participants had a mean age of epilepsy onset of 5.2 years (SD=4.1; range=0-16 years), mean duration of epilepsy of 5.9 years (SD=4.0; range=0.2-14.2 years), and a mean number of previous antiepileptic medications of 2.1 (SD=2.5; range=0-9). The mean age at assessment for the Canadian participants was 11.2 years (SD=2.8; range=6.2-16.4 years). Overall, there are no appreciable differences between the American and Canadian samples for the variables used to determine the severity of epilepsy.

American participants had a mean WISC-IV full scale IQ score of 82.8 (SD=24.1; range=41-132). Nearly one-third of the sample had full scale IQ scores that were below the 2nd percentile (i.e., full scale IQ<70). Clinical norms for full scale IQ in the American sample suggest that it is 'average' for children with epilepsy to have full scale IQ scores between 63 and 101. Canadian participants had a mean WISC-IVCDN full scale IQ of 75.0 (SD=18.7; range=40-109). Having a full scale IQ score below the 2nd percentile was found in 38% of the Canadian sample. Clinical norms for full scale IQ in the Calgary sample suggest that it is 'average' for children with epilepsy to have full scale IQ scores between 59 and 92.

Conclusions: Epilepsy can have a deleterious effect on intellectual growth and development. However, there is considerable value in knowing whether the impact on intelligence in any given patient is consistent with the known effects of epilepsy on intelligence. The information presented in this study will be useful for any clinician who evaluates a child or adolescent with severe epilepsy.

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MATERNAL ANXIETY ABOUT EPILEPSY: ASSOCIATION WITH EMOTIONAL, BEHAVIORAL AND SOCIAL DISTURBANCES

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Rationale: The underpinnings of emotional and behavioral disturbances in children with epilepsy appear to be multi-dimensional, involving both neurological and social factors. There is some evidence that maternal anxiety about epilepsy contributes to lower levels of adaptive functioning in these children, even when seizures are well controlled. In this study we evaluated the relative contributions of maternal anxiety and seizure-related variables to the emotional, social and behavioral characteristics of a group of children and adolescents with intractable focal seizures.

Methods: Fifty children with intractable seizures and their mothers participated in this study. To be included in this study the patient had to be at least 6 years old, English speaking and have a Full Scale IQ greater than 69. Age of the patients ranged from 6 to 19 years. Seizure foci included temporal lobe (55%), frontal lobe (21%) and other (24%). Range of estimated seizure frequency in the previous three months was 0 to 540. Emotional and behavioral functioning was assessed with parent, teacher and self-report measures. These included the Achenbach Child Behavior Checklist (CBCL), Student Behavior Survey (SBS), Children's Depression Inventory (CDI) and Reynold's Child Manifest Anxiety Scale(RCMAS). Predictor variables included seizure frequency, duration of seizure disorder, number of anticonvulsants, Full Scale IQ, maternal education and the Parental Anxiety about Epilepsy Questionnaire (PAEQ). Relationships were evaluated with multiple regression analyses.

Results: Maternal anxiety (PAEQ score) had a significant association with emotional distress as reported by the child, the teacher and the parent. PAEQ explained 9%, 10% and 34% of the variance, respectively. IQ, maternal education and the seizure variables did not contribute to reports of emotional distress. No variable had a significant association with teacher reports of disruptive behavior but PAEQ scores, seizure frequency and number of medications were significantly correlated with scores on the CBCL Externalizing Scale, explaining 33% of the variance. Lower IQ scores were significantly associated with both teacher and parent report of social problems, explaining 15% of the variance for both. PAEQ scores explained an additional 15% of the variance of parent report of social problems.

Conclusions: Maternal anxiety about epilepsy was the strongest and most consistent predictor of reported emotional, behavioral and social problems in children with epilepsy. Lower IQ's contributed, additionally, to social problems. Seizure frequency and number of anticonvulsants increased the likelihood of disruptive behaviors. These findings suggest that parental anxiety about epilepsy should be a target for intervention.

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PROLONGED FEBRILE SEIZURES AND MEMORY DEVELOPMENT

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Rationale: Retrospective studies have highlighted an association between temporal lobe epilepsy and a childhood history of prolonged febrile seizures (PFS). Moreover, imaging studies that have investigated this issue prospectively have found evidence of hippocampal injury following PFS in the form of oedema and increased asymmetry. Given the well established role of the hippocampus in memory, we were interested in investigating whether recognition memory processes were disrupted in a group of children following a PFS. To that end we used the visual paired comparison (VPC) task, which has been commonly used to investigate recognition memory in children. Previous animal work with this task has shown that the tendency to look longer at novel items following a delay relies on the hippocampus. Given the association of hippocampal abnormalities with PFS we predicted that children in the PFS group would show impaired novelty preferences relative to healthy controls.

Methods: Twenty-three children underwent neuropsychological and MRI investigations a mean of 48 days after their PFS episode. The Bayley Scales of Infant Development provided measures of cognition. Intracranial volumes were calculated on the T1 weighted image by using an automatic skull-stripping technique. Two independent researchers traced hippocampal volumes to ensure measurement reliability. For the VPC task, each child was familiarized to one face in five-10 second trials. Following a 5-minute delay, the child saw two memory trials of the familiar face alongside a novel face with the position of the novel face counterbalanced. Looking times were scored off-line from a digital video. Novelty preference was computed as the mean proportion looking to the novel face across the memory trials. Performance was compared to that of 13 normally developing children of similar age.

Results: A univariate analysis of variance test controlling for cognition found that the two groups were different in their novelty preferences ($p=0.01$). Namely, the PFS group spent less time looking at the novel face (0.48) than the control group (0.59) across both memory trials. An independent samples t-test revealed that the PFS group performed worse than controls on cognitive measures ($p=0.05$), yet there was no effect of cognition on their novelty preferences ($p= 0. 57$). A partial correlation within the PFS group controlling for age found that mean hippocampal volumes were positively correlated with novelty preferences ($r=0.46$, $p=0.04$).

Conclusions: In this study we found differences between a group of healthy controls and children following a PFS on a hippocampally dependent task. Namely, patients following a PFS spent less time looking at a novel face following a delay when compared to their normal counterparts. The absence of any relationship between cognitive level and performance on this task despite the group differences in cognition attests to the specificity of the memory impairment exposed by the VPC task. Finally, the relationship between mean hippocampal volumes in the PFS group and their degree of novelty preference corroborates the important role of the hippocampus in these processes.

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NEURODEVELOPMENTAL OUTCOME FOLLOWING EPILEPSY IN INFANCY

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Rationale: Early onset childhood epilepsy is associated with poor neurodevelopmental outcome. Few studies of the natural history exist however; determining predictors of poor outcome is important in identifying those at risk and for developing appropriate intervention strategies. We report data from a prospective population-based study evaluating neurodevelopmental outcome of children with epilepsy onset < 2 years.

Methods: Children < 2 years of age presenting with recurrent unprovoked seizures from a defined area of North London were enrolled over two years. Clinical assessments and neurodevelopmental evaluation were performed at enrolment using Bayley Scales of Infant and Toddler Development-III and at follow-up using the Leiter-R. Neuroimaging and EEG data at presentation were evaluated. Univariate nonparametric statistical analysis (Mann-Whitney, Kruskal-Wallis and Spearman's Rho) were used to investigate developmental outcome in relation to infantile spasms, MRI and EEG.

Results: Of 69 infants enrolled, data from baseline and 3 year follow-up were available for 36 (23 male, age onset M=6.6 m, age follow-up M=49.5 m).At follow-up 61.1% had an IQ > 2SD below the mean. Cognitive baseline scores and follow-up IQ scores were strongly correlated r = 0.758 (36), p < 0.01. The presence or absence of an aetiological relevant finding on MRI was related to IQ: relevant finding (47.2%) M IQ=59, nonspecific abnormality (25%) M IQ= 78, normal (22%) M IQ=92 (p=0.013). Children with epileptiform discharges on EEG or abnormal background with no epileptiform activity had mean IQs (58, 60) significantly lower than children with a normal EEG (105; p = 0.006). Children with a history of infantile spasms (33%) had significantly lower IQ scores at follow up than children with no history (p= 0.043).

Conclusions: 60% children with early onset epilepsy are developmentally delayed 3 years following initial presentation. Developmental status close to presentation predicts function at follow up. Aetiologically relevant structural brain abnormalities, epileptiform activity and abnormal background activity on initial EEG, and a history of infantile spasms were associated with significantly lower IQ scores.

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LANGUAGE PERFORMANCE AND WORKING MEMORY IN CHILDREN WITH ROLANDIC EPILEPSY

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Rationale: In clinical practice, there seems to be a correlation between language outcome and Rolandic epilepsy, language outcome seems to be impaired in these children. In this study we measured language outcome of children with Rolandic epilepsy and correlated these results on the working memory-model of Baddeley.

Methods: Retrospective patient file study of 48 children (mean age 115 months, SD 19.7) with Rolandic epilepsy. These children were thoroughly evaluated on the epilepsy centre Kempenhaeghe, the Netherlands. All children had a 24 hour electroencephalogram and a neuropsychological assessment. Furthermore, questionnaires were given to the parents and the teachers of these children to measure the behaviour and the subjective expected school performance by them.

Results: In children with Rolandic epilepsy, parents report their children to have more language problems, like reading, writing and perception and expression of language. There was a significant delay in months on the established reading skills at school (words mean delay in months 6.0 SD 11.9, p<0.002, sentences mean delay in months 8.6 SD 12.7, p<0.000), but not on the reached mathematics skills at school (mean delay in months 4.1 SD 12.5). Semantic language performance is more impaired in children with Rolandic epilepsy (mean delay of 8.6 months SD 12.7). The phonological loop was not impaired (mean score digit span WISC 9.2 SD 3.4).

Conclusions: Language is impaired in children with Rolandic epilepsy. Our results suggest that this is not depending on the phonological loop or on the central executive component of the widely accepted working memory-model of Baddeley. Semantic language skills are more impaired than phonological language skills. Reading disorders are frequently noticed by the parents of children with language impairment. Children with Rolandic epilepsy should be screened for being at risk for reading problems.

1.375

RESPONSE TO HIGH DOSE DIAZEPAM CHALLENGE TEST IN ELECTRICAL STATUS EPILEPTICUS OF SLEEP (ESES)IN CHILDREN

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Rationale: ESES is an age dependent epileptic encephalopathy characterized by significant activation of epileptiform activity in the sleep EEG. Different treatment modalities are associated with variable success.High dose diazepam challenge test is used to identify suitable patients for nocturnal high dose diazepam maintenance therapy. Our objective is to quantify the effect of high dose diazepam on the sleep EEG of children with ESES and to identify the variables that correlate with the EEG response.

Methods: Inclusion criteria:

1. Children aged 3-12 years diagnosed with ESES during May 2008-June 2010

2. ESES defined as spike-wave index (SWI) of >85% during sleep or >50% if the awake EEG showed a SWI of <20%

Exclusion criteria:

1. Known 'myoclonic' epilepsy syndrome (Eg: Lennox-Gestaut syndrome)

2. On Carbamazepine/oxcarbazepine in the preceding 2 months.

1mg/kg of Diazepam (maximum 40 mg) was given in 2 equal half doses 2 hours apart in the late evening PO or PR. Sleep SWI was calculated after the second dose of diazepam. Good response was defined as decrease in sleep SWI by >50%.

Results: Of the 15 children with ESES (Table 1), 11 had diazepam challenge test. Six (55%) had a good response. Sex or age of onset of ESES was not associated with EEG response. Delay in administering diazepam after onset of ESES was significantly greater in the non-responder group (Responders: Mean 0.42 yrs with SD 0.24; Non-responders: Mean 4.5 years with SD 3.3; unpaired t-test p=0.01). Duration of ESES significantly correlated with EEG improvement, greater improvement with shorter duration of ESES (duration of ESES Vs pre-post DZP SWI; Pearson correlation: $r^2 = 0.297$, one sided p= 0.04)

Conclusions: In children with ESES, good EEG response following high dose diazepam challenge test is associated with shorter duration of ESES. This findings needs to be validated by a large prospective cohort.

IMAGE: tables/907853_T1.jpg

Table 1 Data on the Diazepam challenge test

IMAGE: tables/907853_T2.jpg

M-Male, F-Female, Yrs- Years, L-Left, R-Right, Dx-Diagnosis, DZP-Diazepam, SWI- Spike Wave Index, ND- Not done, NA- Not applicable. G- Generalized, F- Focal, Onset of ESES designated abitrarilly as 2 years of age in 'early global delay'. In #12, duration of ESES was considered as 0 for calculation.

1.376

THE EFFECTS OF EPILEPSY SURGERY IN CHILDREN ON EVERYDAY MEMORY FUNCTION

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Rationale: Children with intractable epilepsy are at risk for memory impairment. This study examined parent report of their child's everyday memory function before and after epilepsy surgery. It also investigated a number of variables to identify potential predictors of change in everyday memory after surgery.

Methods: Parents reported on their child's everyday memory function using a 27-item rating scale, before and approximately one year after surgery (n = 43; mean age = 12.3 years). A non-surgical comparison group (n = 19; mean age 13.2 years) was evaluated at similar points in time. The location of epileptogenic tissue, age of seizure onset, duration of epilepsy, number of antiepileptic medications and premorbid IQ were investigated as possible predictive variables for everyday memory performance.

Results: The two groups did not differ on age, sex distribution, age at seizure onset, number of anti-epileptic medications, or handedness. An ANOVA on questionnaire scores revealed an interaction between time and laterality. Left hemisphere resections resulted in a mild decline in everyday memory scores whilst right hemisphere resections resulted in an improvement. These changes for both groups were, however, quite modest in degree. There was no change over time in the comparison group. The main predictors of change in everyday memory in the surgical group were age at baseline such that older children showed the most improvement, and duration of epilepsy such that individuals who had epilepsy for longer periods of time showed the most improvement. There were no significant changes related to seizure outcome in the surgical group.

Conclusions: The present study is the first to demonstrate that everyday memory function in children may be differentially affected by resections from the left and right hemispheres of the brain. There appears to be some plasticity involved for everyday memory function, as indicated by correlations with age and duration in the surgical group.

1.377

ANXIETY AND DEPRESSION SYMPTOMS IN CHILDHOOD ABSENCE EPILEPSY

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Rationale: Childhood absence epilepsy (CAE) is a neurological condition that typically has onset between the ages of 4 and 8 in children, accounting for 2% to 8% of patients with epilepsy. CAE seizures consist of brief, abrupt staring spells in which the child is unresponsive and usually lasts less than 10 seconds. Growing research is rebutting the notion of CAE as a benign syndrome. Psychosocial, behavioral, and emotional problems have been identified in CAE at a greater rate than healthy peers, with many of the same issues persisting into adulthood despite disease remission by late adolescence. Long-term difficulties associated with co-morbid anxiety and depression are of particular concern for practitioners.

Methods: The current study aimed to delineate differences in symptoms associated with anxiety and depression among CAE and healthy controls (HC) using the Behavior Assessment System for Children Parent Rating Scales (BASC-PRS), a comprehensive measure of a child's adaptive and problem behaviors in community and home settings. Subjects were recruited from the community via advertisements or referral from their neurologist. Our cohort consisted of 45 CAE and 42 HC subjects (ages 6-16) that were matched for age, sex, and socioeconomic status using t-tests or Chi-square comparisons. Socioeconomic status information was obtained via self-report using the Hollingshead Four Factor Scale. The BASC-PRS and the Wechsler Abbreviated Scale of Intelligence (WASI) were administered to all subjects, and group differences were analyzed using Kruskal Wallis test and independent sample t-tests.

Results: No significant differences were found between groups in regards to age, gender, socioeconomic status, or intelligence. Statistical differences between the groups were found on both global scales of the BASC-PRS associated with Anxiety ($p < 0.001$) and Depression ($p = 0.005$). Item analysis within the Anxiety Scale revealed a number of significant group differences, including items specific to "worries," "worries about things that cannot be changed," "worries about what teachers think," "says: I'm not very good at this," and "is nervous." Depression items such as "cries easily," "says: nobody understands me," "is easily upset," and "is sad" were also significantly increased in the CAE group.

Conclusions: Our findings suggest greater prevalence of a number of symptoms associated with increased anxiety and depression in CAE patients as compared to healthy counterparts. Many of the behaviors observed by parents are considered core symptoms of these conditions, and are often more chronic in nature, thus negatively impacting long-

term development. These findings add to the growing literature stressing the importance of early identification and management of behavioral, emotional, and psychosocial factors associated with CAE in order to maximize quality of life and functional outcomes.

1.378

SOCIAL BEHAVIOR IN CHILDREN WITH EPILEPSY: WHAT DO THEIR TEACHERS THINK?

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Rationale: Difficulties with social functioning are reported in children with epilepsy. There have been no prior studies on how teachers perceive the social skills of children with epilepsy. We, therefore, assessed social behavior in children with epilepsy as reported by their teachers, who observed them in their social interactions on a daily basis over time.

Methods: Twenty three teachers of children 9-11 years old with established epilepsy who spent at least 50% of there time in a normal classroom were asked to complete the Social Skills Improvement System (SiSS). The questionnaire assesses total social skills (communication, cooperation, assertion, responsibility, empathy, engagement and self-control), total problem behaviors (externalizing, bullying, hyperactivity/inattention and autism spectrum), and academic competence. Total scores and subscales were compared to normative data using a one-sided t-test and Sidak correction for multiple comparisons.

Results: All teachers (100%) completed the SiSS. They reported significantly poorer total social skills (p= 0.017) compared to normative published data. Specifically, they noted lower levels of assertion (p= 0.056) and less engagement (p= 0.002). Teachers described difficulties initiating behaviors such as asking others for information, introducing oneself, responding to the actions of others, joining in activities in progress, initiating conversations, making friends and interacting well with other. Teachers did not document increased problem behaviors however they noted increased autism spectrum symptoms (p= 0.058). They described children with epilepsy as interacting poorly, not taking part in conversations, making odd gestures and becoming upset at changes in routine or having nonfunctional routines. Their responses also indicated lower academic competence (p= 0.001).

Conclusions: In addition to prior studies on parent reports, this study demonstrates that teachers also observe significantly poorer social skills and academic performance in children with epilepsy. The association with autism spectrum symptoms emphasizes a need for studies to determine the role that both epilepsy and autism spectrum variables play in the poor social skills of these children. Our findings, limited by a small sample, suggest that social difficulties in children with epilepsy are also recognized within the school environment. They also set the groundwork for understanding social difficulties these children experience with their peers in the classroom environment.

1.379

PSYCHOLOGICAL PROFILE OF EPILEPTIC CHILDREN AND ADOLESCENTS

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Rationale: This study investigated the influence of epilepsy on the level of adaptive function, emotional and behavioral problems, and quality of life in children and adolescents with epilepsy.

Methods: A clinician rating and parent-report scales were administered to 594 children and adolescents(boys=372, girls=251), aged 1 to 18 years. Parents provided behavioral, emotional and adaptive information on each clinician rating index and behavior checklist.

Results: While developmental quotient had a tendency of negative correlation with age, adaptive functions showed improvement as getting older. On behavioral and emotional domains, academic and social competence had the lowest score but also had a tendency of improvement by growing, on the other hand, withdrawn was getting worse by growing up, especially in girls group. Over all age, the quality of life relatively belonged to quite good level of satisfactions, excepting cognitive and social functions such as concentration, memory, language, social activities and social interactions, showing better satisfactions by aging. Generally in the oldest group, adaptive functions and quality of life showed the highest scores, and the lowest behavioral and emotional problems, despite negative correlations of development level and age. Children with epileptic encephalopathy, multiple AEDs, and/or medical intractability showed relationship with abnormal behaviors.

Conclusions: Children with epilepsy in younger age were shown to have more vulnerability to behavioral, emotional and adaptive problems. Cognitive and social function were the most lasting problems of children and adolescents with epilepsy.

Descriptive data_Age and Sex

IMAGE: tables/905576_T1.jpg

Age group comparison_Adaptive and Developmental level

IMAGE: tables/905576_T2.jpg

1.380

MEMORY IMPAIRMENT OF CHILDREN WITH TEMPORAL LOBE EPILEPSY IS AT LEAST PARTIALLY EXPLAINED BY THE EXECUTIVE DYSFUNCTION

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Rationale: Executive functions are essential for good information encoding and storing as well as to mental organization. Therefore, it is reasonable to postulate that executive dysfunction (ED) may aggravate memory impairments. Memory deficits are well-established in patients with temporal lobe epilepsy (TLE). ED have also been demonstrated in these patients. However, the relationship between ED and visual and verbal memory have not been investigated yet. We aimed to characterize memory and executive functioning in children with TLE and to evaluate the impact of ED in memory tasks.

Methods: For this purpose, we evaluated 36 children and adolescents (11.78 years-old; SD 2.26) with TLE and 28 healthy volunteers (11.96 years-old; SD 2.30) using a comprehensive battery composed of tests of episodic and semantic memory, learning, attention (concentration, selective and divided attention), mental flexibility and, mental tracking. Four analyses were conducted: (i) comparison between patients and controls in memory tests; (ii) comparison between patients and controls in executive functions tests; (iii) correlation between memory and executive functions tests and, (iv) comparison between patients with mild/moderate ED and severe ED in memory tests.

Results: Children with TLE had worse performance in immediate ($p=0.046$) and delayed ($p=0.048$) Story Memory and in Sentence Memory ($p=0.002$). As to executive functions, patients showed impairments in Trail Making B errors ($p=0.016$); WCST categories achieved ($p=0.018$) and number of non-perseverative responses ($p=0.046$); Verbal Fluency ($p=0.048$) and Number and Letter ($p=0.005$). Planning, abstraction and mental tracking were not correlated to memory tasks. All attention domains and working memory were correlated with visual and verbal memory. Patients with severe ED had worse performance in Scenes Memory ($p=0.032$); Design Memory ($p<0.001$); immediate ($p=0.002$) and delayed Story Memory ($p=0.003$); Sentence Memory ($p<0.001$); Verbal ($p=0.010$) and Visual ($p=0.048$) Learning.

Conclusions: Children and adolescents with TLE have memory and executive dysfunctions. Moreover, there is an impact of ED in the performance of memory tests, that could be demonstrated both with the correlation of memory and executive functions tests and with the worse performance of patients with severe ED in memory tests. Therefore, clinicians should be aware that evaluation and rehabilitation programs for memory in patients with TLE must take into consideration executive functions.

1.381

SEMANTIC KNOWLEDGE LOSS IN PATIENTS WITH ADULT ONSET COMPLEX PARTIAL SEIZURES AFTER LEFT ANTERIOR TEMPORAL LOBE RESECTION

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Rationale: Semantic knowledge refers to facts about the world acquired through experience. Among individuals who undergo left anterior temporal lobe resection (ATR) for control of complex partial seizures (CPS), those who have greater presurgical semantic knowledge are at the greatest risk for postsurgical decline of semantic knowledge. Patients with greater presurgical semantic knowledge are often those whose seizures started later in life. Individuals with seizure onset in childhood or in teenage years can also adequately learn factual information over the course of their lives. The present study evaluated change in semantic knowledge from before to after ATR in two groups: patients with age at onset of CPS in childhood or as a teenager (<18 years-old) versus patients with age at onset of CPS as an adult (18+ years-old).

Methods: Ninety-eight individuals who underwent unilateral ATR (43 left, 55 right) participated in the study. Mean age of childhood/teenage onset CPS was 9.6-years (range from 3-month-old to 17-year-old), and 26.6-years for the adult onset CPS group (range from 18 to 44-years-old). The Boston Naming Test (BNT) was used to quantify semantic knowledge.

Results: There was no statistically significant difference in chronological age between the groups at the time of surgery (mean age for childhood/teenage group = 31 years-old at time of surgery; mean age for adult group = 35-years-old at time of surgery). Repeated measures ANOVA indicated a significant side of surgery by age group interaction for semantic knowledge as a function of time ($F[1,94]=4.38$, $p=0.039$). The largest decline in semantic knowledge after surgery was for individuals with adult onset CPS who underwent left-ATR (see Figure below; this group lost an average of 9 words after surgery). Based on the Reliable Change Index method, 62% of left-ATR patients with adult onset showed meaningful declines in semantic knowledge versus 30% of left-ATR patients with childhood/teenage onset and 5% of right-ATR patients.

Conclusions: The risk of semantic knowledge loss is greatest in adult onset CPS after left-ATR. Presurgical counseling and postsurgical rehabilitation referrals may benefit patients who undergo left-ATR.

IMAGE: images/906776_A.jpg

1.382

SEIZURE RECOGNITION DURING INPATIENT VIDEO/EEG MONITORING

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Rationale: Our goal was to evaluate by behavioral testing during and after seizures whether deficits in memory, language, and consciousness are correlated with underreporting of seizures, and relate these deficits to seizure type and anatomical site of seizure onset.

Prior work suggests that seizures originating in the dominant hemisphere are more likely to go unrecognized, and that impairment in consciousness play a role in seizure awareness. Little work has been done to directly measure attention, language, and memory performance during seizures of different types, to determine which seizures present the highest risk of not being recognized. Knowledge of which seizure types and localizations cause the greatest risk for seizure unawareness will provide useful information for clinicians treating patients, and can also help reveal the mechanisms of impaired function.

Methods: Twenty nine patients who underwent presurgical evaluation in a Video/EEG (VEEG) monitoring unit were recruited. Responsiveness during seizures was assessed retrospectively by reviewing the patient behavior on the video data captured during the monitoring session. For comparison with objective data obtained through VEEG monitoring, we used 3 testing instruments to evaluate patient subjective report of seizures: 1. Admission questionnaire; 2. Patient seizure log; 3. Daily seizure questionnaire. The admission questionnaire was given once to all patients to assess their self perception of seizure awareness. Patients then received a seizure log where they were asked to note any seizure or unusual sensation they may have experienced during the monitoring session. The daily seizure questionnaire was administered once daily and contained questions carefully chosen to determine patient's awareness of seizures that occurred in the past 24 hours. We took into consideration possible clues (such as being told by family members or staff) that may have helped patients realize that they had a seizure.

Results: Patients who had no seizures, did not finish the questionnaires, or had non-epileptic seizures were excluded from the analysis. Data from a total 16 patients were included in the study. Overall, 64 seizures were recorded (24 simple partial seizures, 22 complex partial seizures, 4 secondary generalized seizures and 14 unclassified). Patients were unaware of 47% of all recorded seizures. Seventy three percent of all complex partial seizures were not reported. In contrast, only 8% of all simple partial seizures were not reported ($\div 2 = 19.983$, $p < 0.001$). Five of six patients who reported on their admission questionnaire to be perfectly aware of their seizures actually were perfect documenters.

Conclusions: This study demonstrates that almost half of all recorded seizures during inpatient VEEG monitoring are unrecognized by the patients. Impaired consciousness during seizures appears to be one of the main factors that influence patient ability to recognize and accurately report their seizures. Further study is needed to investigate to what extent altered memory function or language impairment may participate in reducing patient seizure report.

1.383

SOCIAL AND PSYCHOLOGICAL OUTCOME OF EPILEPSY IN WELL-FUNCTIONING CHILDREN AND ADOLESCENTS 10 YEARS AFTER DIAGNOSIS

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Rationale: A population based study of epilepsy in children from a Swedish county was published in 2006 (Larsson K, Eeg-Olofsson O. Eur J Paediatr Neurol 2006;10:107-13). From this material well-functioning children treated for epilepsy in January 1997 (n=47) were invited 10 years later to participate in a study to investigate the outcome from medical, social and psychological aspects. The first part, in which 45 individuals participated, described mainly the medical outcome, while this second part describes social and psychological outcome.

Methods: An integral system of multi-informant assessment , ASEBA (Achenbach System of Empirically Based Assessment), was used to assess diverse aspects of adaptive and maladaptive functioning and is a further development of behaviour checklists. Check lists and self-reports were sent out to the 45 individuals and their parents.

Results: The response rate was 69%. Thus, 31 individuals, 19 females and 12 males aged 11-22 years were evaluated. All information received was computer scored. Seven were <18 years (group 1) and 24 e" 18 years (group 2). At the end of the 10-year period 21 (68%) were seizure free. Four children were still in nine-year compulsory school, 10 attended senior high school, and 17 had passed this stage. Out of the last-mentioned, eight studied at university, six were employed, and 3 sick-listed. Seven types of behavioural/emotional problems were found (23%), one in group 1 had four different problems, and one in group 2 had two. Internalizing symptoms as anxious/withdrawn-depressed and somatic complaints were seen in both groups. An externalizing symptom as aggressive behaviour was found in group 1. Attention and thought problems were found in group 2 and social problems in group 1.

Conclusions: In well-functioning individuals with childhood onset epilepsy there are few deviating results in just a few individuals. Maladaptive functioning, especially internalizing symptoms, was found. Such symptoms are often found in longitudinal population based studies of both children and adolescents with epilepsy.

1.384

LINGUISTIC PERFORMANCE AND INTEGRITY OF THE ARCUATE FASCICULUS IN NON-LESIONAL EPILEPSY

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Rationale: Lesion studies of the arcuate fasciculus (AC) indicate that this white matter pathway is a critical component of the linguistic network. It is also known that linguistic performance is often compromised in patients with non-lesional epilepsy. The goal of this diffusion tensor imaging (DTI) study was to explore the relation between the epilepsy, the functional integrity of the AC and the linguistic performance in the patients with non-lesional epilepsy.

Methods: Twenty two epileptic patients with no apparent lesions on structural brain imaging (normal MRIs) underwent DTI analysis of the AC and neuropsychological testing.

Results: The results show a high correlation between FA values in the left AC and some language and reasoning tasks (vocabulary, similarities and matrix reasoning). An analysis of variance was also carried out to check whether the FA values of the AC were affected in the hemisphere of seizure origin. The results showed that the patients had higher FA values in the left AC, regardless the origin of the seizure (left, right or both hemispheres).

Conclusions: This study advances our understanding of how the epilepsy may affect the white matter pathways and the performance of the patients in neuropsychological tasks even in absence of evident brain injury.

1.385

EARLY LIFE SEIZURES LEAD TO COMPENSATORY INCREASES IN PREFRONTAL CORTEX THETA POWER TO MAINTAIN COGNITIVE PERFORMANCE IN ADULTHOOD

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Rationale: Early life seizures (ELS) in neonates cause long-term cellular changes in the brain, and carry cognitive consequences later in life. ELS cause long-lasting alterations in inhibitory transmission, which drive neuronal oscillations (EEG rhythms) that are important for cognitive processes. We propose that one of the mechanisms by which ELS induce cognitive impairments is through a disruption of neuronal oscillations. We simultaneously recorded theta (4-12Hz) and gamma (30-100Hz) oscillations in the hippocampus (both CA3 and CA1) and in the prefrontal cortex (PFC) in adult ELS rats performing a memory task called delayed-non-match-to-sample (DNMS). We hypothesized that decreased performance would be associated with alterations of oscillation amplitude and synchrony within and across structures.

Methods: Five control rats and three ELS rats (exposed to 100 flurothyl seizures from days P15-30) were trained on the DNMS task in adulthood (P55-100). This short-term memory task involves both hippocampal and prefrontal structures. Local field potentials were recorded in vivo during all training sessions with depth electrodes in CA3, CA1, and PFC. Power and coherence were calculated dynamically with sliding windows (1s for theta; 0.2s for gamma) using Fourier analysis. Logistic regression and ANOVA statistics were used to compare power and coherence relative to performance.

Results: Among 8 rats, 7926 trials were analyzed. ELS rats took significantly longer to learn the DNMS task ($p<0.05$), but eventually reached control performance levels as training progressed. ELS rats had a striking 30% increase in PFC theta power over controls during the trials (but not between trials), and this increase was significantly more prominent in correct trials. Correct trials were also accompanied by elevated CA3, and decreased PFC, gamma power in ELS rats. In addition, their CA1/PFC theta coherence was higher during the memory encoding period ($p<0.001$), but was not predictive of performance. Finally CA3/CA1 gamma coherence during retrieval was predictive of errors in all rats ($p<0.001$).

Conclusions: These results show that cognitive deficits observed in adult rats that were exposed to ELS can be improved with training. This is paralleled with alterations in PFC theta power, and CA3 and PFC gamma power, which are predictive of performance. Together, this suggests that modified oscillatory patterns may participate in compensatory mechanisms that restore cognitive function in ELS rats. These data highlight the relevance of network oscillations in seizure-induced cognitive impairment.

1.386

RIGHT SIDED RECEPTIVE LANGUAGE DOMINANCE IN MEDICALLY REFRACTORY RESECTIVE EPILEPSY SURGERY CANDIDATES: AN MEG STUDY WITH MULTIPLE LANGUAGE TASKS

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Rationale: Patients with medically refractory partial seizures who are candidates for resective epilepsy surgery frequently undergo language mapping as to minimize resection of eloquent cortex. Unique representation of language in Epilepsy patients especially these with childhood onset of seizures may alter the surgical approach.

Methods: We used a large array 148 channel biomagnetometer (4D Neuroimaging)and tasks tapping receptive (word recognition) and expressive(verb generation,picture naming) language mapping paradigms on 6 Medically Refractory Resective Epilepsy Candidates and 12 controls.Language activations were assessed utilizing standard methods with Single Equivalent Current Dipole (SECD)that clustered in time and brain space. A laterality index(LI) was calculated on SECD meeting criteria [(L-R)/(L+R)] for each patient.Neuropschological testing was performed on all patients. 4/6 had angio-WADA and direct cortical stimulations. Healthy controls (N=12) underwent an MEG study with a word recognition language paradigm. Language activation was similarly assessed with SECD fits and calculation of LI.

Results: Of the six epilepsy patients 5/6 showed right hemispheric or bilateral language dominance for receptive language. In contrast 10/12 of control patients showed left hemispheric or bilateral dominance for receptive language. Expressive language was left hemispheric in all the epilepsy patients. Age of seizure onset had a range of 18 months-17 years.

Conclusions: Receptive and Expressive language may have divergent hemispheric dominance in patients with Medically Refractory Epilepsy with childhood and adolescent onset of seizures. The right sided receptive language hemispheric dominance in epilepsy patients may have implications for surgical planning as well as emphasize the need to separately assess both receptive and expressive language in these patients. MEG with multiple language tasks can be used non-invasively to assess language in both hemispheres A larger cohort of patients is needed as to substantiate these preliminary findings.

1.387

COGNITIVE AND AFFECTIVE FUNCTIONS IN ADD-ON THERAPY WITH LACOSAMIDE

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Rationale: In antiepileptic drug intervention, unwanted cognitive and affective side effects may seriously compromise the patient‘s quality of life, his compliance and his ability to work. Therefore, individual cognitive and mood changes should be tracked through the course of drug therapy. Lacosamide is one of the newer antiepileptic drugs used in the treatment for partial-onset seizures. In this study, cognitive and mood side effects of add-on therapy with lacosamide were investigated.

Methods: 18 epilepsy patients were investigated. In addition to their pre-existing, stable antiepileptic medication, lacosamide was titrated as an add-on therapy. The patients underwent an examination of their cognitive and affective functions before add-on of lacosamide and three months after. The computerized neuropsychological test battery (CCTE) covered the cognitive domains of attention, cognitive speed, working memory, verbal and figural memory. Emotional variables like

depression, anxiety, irritability, sleep quality and subjective performance were recorded by means of visual scales.

Results: No significant changes of the patients‘ cognitive and mood profile related to the add-on of lacosamide could be detected. Comparing the two examinations before and after titration of lacosamide, median to high correlations were proven for all subtests of cognitive performance ($p<0.05$) and affective state ($p<0.01$). In most cognitive subtests a slight but not significant improvement was shown, which might be interpreted as practice effect.

Conclusions: The results show that with lacosamide as an add-on antiepileptic therapy, no significant changes occur in the cognitive or mood profile. It indicates that, concerning cognitive and affective side effects, lacosamide as an add-on medication is a well-tolerated antiepileptic drug and is unlikely to impair cognition and mood. In general, a regular neuropsychological assessment of these functions is essential to keep track of unwanted side effects of antiepileptic medication and to optimize therapeutic interventions.

1.388

FACTORS UNDERLYING DISCORDANT RIGHT HEMISPHERIC LANGUAGE CLASSIFICATION ON WADA-CONFIRMED LEFT DOMINANT PATIENTS

Ann M. Hempel[1,2] and G. L. Risse[1,2] ([1]Minnesota Epilepsy Group, PA, St. Paul, MN and [2]Neurology, University of Minnesota, Minneapolis, MN)

Rationale: Functional imaging studies are increasingly being used to determine hemispheric language lateralization prior to epilepsy surgery. However, concern remains regarding validity of noninvasive procedures given a minority of patients who have demonstrated discordance between hemispheric dominance based on the Wada procedure and functional imaging. The goal of this study was to examine the basis of the discordance in language lateralization between the Wada procedure and magnetic source imaging.

Methods: The sample included 19 patients ages 13-60 years who demonstrated left hemispheric dominance on the amobarbital procedure, and demonstrated a temporal lobe seizure origin on EEG. Those who were classified as MSI right hemisphere language dominant (n=6; MSI-R) were compared to those who were classified as MSI left hemisphere language dominant (n=13; MSI-L) on the following variables: presence of language impairment (Wechsler VC d” 85 and Boston Naming Test d” 45 raw or standard score < 70), presence of verbal memory impairment (word list delayed recall d” 8), early age of seizure onset (d” 5 years), presence of satisfactory right hemispheric memory capacity on IAP(> 50% recognition), right versus left temporal seizure onset, and presence of a left mesial temporal structural lesion. Results were analyzed using the Fisher’s Exact Test.

Results: Patients who displayed MSI-R were more likely to evidence language impairment (p=.003), satisfactory verbal memory (p=.057) and early age of seizure onset (p=.057) than those who displayed MSI-L. Groups did not differ in presence of a left mesial temporal structural lesion, side of seizure onset, or IAP right hemispheric memory capacity.

Conclusions: For those who demonstrate clear left hemisphere dominance on the Wada test, discordant classification of MSI appears to be associated with impaired language function and early age of seizure onset. These factors have previously been associated with diminished integrity of the language dominant hemisphere. This might account for underestimation of the role of the left hemisphere in language processing by MSI.

1.389

RELIABILITY OF THE INTRACAROTID AMOBARBITAL PROCEDURE (IAP)

Chris Morrison[1], L. A. Whitman[1], C. E. Carlson[1], T. Becske[2,1] and w. B. Barr[1] ([1]Neurology, NYU Langone Medical Center, New York, NY and [2]Radiology, NYU Langone Medical Center, New York, NY)

Rationale: The IAP is widely used to assess language and memory prior to resective neurosurgery. On occasion, it is repeated due to procedural difficulties (e.g., drowsiness/poor cooperation) or clinical need (e.g., years lapsed between the initial IAP and the time of surgery). We reviewed our experience with repeating this procedure to better understand IAP reliability.

Methods: A review of the NYU CEC patient registry (2001-2009) revealed 562 IAPs with 16 individuals (6 men) having repeated IAPs. There were two children, ages 5 and 11; adult ages ranged from 20-60 years at the time of their first IAP. Educational experience ranged from attendance to a special needs school to having completed Master’s degrees. General intellectual level paralleled this diversity with individuals performing across the spectrum from “Deficient” to “Above Average”. Age of seizure onset ranged from 11 months to 49 years. At the time of the first IAP, there were 14 subjects with left hemisphere seizure onset, one with a right sided focus, and one had bilateral independent foci. Reasons for repeating the IAP included procedural difficulties (6), patients considering a first (3) or second (4) surgery years after their first IAP, and the first IAP results were the “wrong way” (3). The inter-IAP-interval was quite variable (1 month to 15 years).

While most IAPs were performed at NYU, some patients had undergone an IAP elsewhere. Thus, the language and/or memory scoring systems were slightly different across procedures which limited direct comparison. Therefore, for each hemisphere injected, the final criterion for language localization (left, right, or bilateral) and memory functionality (“pass” or “fail”) were recorded. One patient had 3 IAPs, 3 patients had either a 3rd injection during one of their procedures or did not have both hemispheres retested during the second IAP, and for one patient, the language but not the memory data were available for one IAP. Thus, there were a total of 14 ipsilateral and 17 contralateral injections reviewed.

Results: Language functioning was consistently localized (11 L, 2 R, and 2 bilateral) in all cases. In terms of memory, 86% of the ipsilateral and 71% of the contralateral pass/fail outcomes were consistent across procedures. A Yate’s corrected chi square was significant for ipsilateral (p=.05) but not for contralateral (p=.29) injections. When just the 6 patients who underwent repeat IAP due to technical difficulties were reviewed, 100% consistency was seen across procedures.

Conclusions: Language lateralization findings were robust and unchanged regardless of the indication for repeat IAP. Interestingly, while procedures repeated for “technical reasons” showed no change in memory ability (despite such things as reduced dose and improved alertness), “technically valid” IAPs that were performed following the natural clinical course of epilepsy or surgical intervention showed the most change. Therefore, rather than assume that test-retest variance is due to unreliability of the procedure, it is possible that the IAP on repeat administration is detecting unique information about changes in brain functionality.

Ipsilateral

IMAGE: tables/901228_T1.jpg

Contralateral

IMAGE: tables/901228_T2.jpg

1.390

'OUT-OF-BODY EXPERIENCE' DURING EXTRA-OPERATIVE CORTICAL STIMULATION OF RIGHT PRECUNEUS: A NOVEL OBSERVATION

Ahsan Moosa Naduvil Valappil, J. Bulacio, D. Nair and I. Najm (Epilepsy Center, Neurological Institute, Cleveland Clinic, Cleveland, OH)

Rationale: Out-of-body experience (OBE) is frequently described as a feature of near death experience in post cardiac arrest survivors. Similar phenomenon has been reported in patients with epilepsy, and migraine. Rare reports of OBE with cortical stimulation have been documented. Most of these reports indicate involvement of the non dominant lateral temporo-parietal junction. We report a patient with OBE during extra-operative cortical stimulation of the right ('non-dominant')precuneus. Precuneus has not been recognized previously as a potential generator of OBE.

Methods: A 35-year-old, right handed woman, had intractable epilepsy from the age of 12 years. Non invasive evaluation suggested right frontal lobe epilepsy. She underwent intracranial EEG monitoring using subdural grids in the fronto-temporal and medial parietal regions. Seizure onset was localized to the right superior and middle frontal gyrus. She became seizure free following resection of right superior and middle frontal gyri, she remained seizure free at 2-year-follow up. Cortical stimulation was performed pre-operatively to identify eloquent areas in the frontal and medial fronto-parietal regions.

Results: On stimulation of the anterior part of right precuneus, at 6 mA, patient reported subjective out-of-body experience. She reported: "I just feel the same thing again…I know everybody is here… but I don't feel like I am in the room…I feel like I am watching down from above… I feel very detached…I feel disconnected from every one in the room…". The same subjective experience was reproduced with repeat stimulation, performed an hour later. OBE was not part of her seizure semiology. Out-of-body experience following cortical stimulation of right (non dominant)lateral temporo-parietal junction has been well documented. There are no previous reports of OBE elicited from precuneus. In one previous report of PET study performed during OBE elicited by cortical stimulation of right temporo-parietal junction, simultaneous activation of the inferior parietal lobule and ipsilateral precuneus was noted. Findings in our patient also support a role for precuneus in the generation of OBE.

Conclusions: We report out-of-body experience elicited by electrical stimulation of right anterior precuneus. This finding is at variance from earlier observations of out-of-body experience with stimulation of non dominant lateral temporo-parietal junction. Connections between the non dominant temporo-parietal junction and ipsilateral precuneus may be important for the generation of out of body experience.

1.391

DOES CONSCIOUSNESS OCCUR IN "FRAMES"? EVIDENCE FROM INTRACRANIAL EEG RECORDINGS

S. Pockett[1], B. Brennan[1], G. Bold[1] and Mark D. Holmes[2] ([1]Physics, University of Auckland, Auckland, New Zealand and [2]Neurology, University of Washington, Seattle, WA)

Rationale: We investigate the possibility that consciousness occurs in discrete chunks or frames by examining the repetitive instants when brain EEG analytic power approaches zero, thus acting as shutter for a cinematographic theory of consciousness.

Methods: We compare the frequency of putative chunks of consciousness reported in earlier behavioral literature with the frequency of deep analytic power minima in both (1)

mathematically generated power-law noise and (2) intracranial EEG recorded from conscious and unconscious human subjects. 30 sec segments of EEG recordings were studied in four subjects with refractory epilepsy who underwent intracranial, subdural, 8x8 64 contact grid recordings to localize epileptic seizures. "Conscious" EEG segments were taken during time periods when the subjects were alert and awake, and the EEG was free of seizures or epileptiform discharges. "Unconscious" EEG was obtained from the immediate post-ictal period following generalized tonic-clonic convulsive seizures.

Results: A good fit is observed between the behavioral measurements and both sorts of analytic power measurements.

Conclusions: We hypothesize that the episodic nature of the analytic power generated by the brain (a) arises from underlying physical or mathematical laws rather than from any specifically biological process, but nevertheless (b) constrains consciousness to occur in discrete chunks or cinematographic frames.

Saturday, December 4, 2010

Investigators' Workshop Saturday Evening Session
6:00 p.m.-8:00 p.m.

IW.01

PEPTIDOPATHY, CHANNELOPATHY OR BAD NETWORK - WHAT CAUSES EPILEPSY IN ALZHEIMER'S DISEASE?

Asla Pitkanen[1] and Helen Scharfman[2] ([1]Neurobiology, University of Eastern Finland, Kuopio, Finland and [2]The Nathan Kline Institute, New York University, New York, NY)

Summary: For a long time, patients with Alzheimer's disease (AD) have been known to have myoclonic seizures. Recently it was shown that the risk of unprovoked partial or generalized seizures is increased up to 86-fold in patients with an early onset of AD. Moreover, it was hypothesized that daily cognitive fluctuations in AD could relate to the occurrence of undiagnosed complex partial seizures. Recently, many different mouse strains that overexpress mutated form of amyloid precursor protein (APP), show spontaneous seizures and have interictal epileptiform discharges. These studies raise questions: what triggers multiple seizure types or hyperexcitability in AD? Recent data suggest that amyloid precursor protein (APP) cleavage products may be involved because they can modulate several ion channels. Furthermore, enzymes contributing to APP processing may use Na-

channel subunits as substrates, and consequently, affect Na-channel trafficking and composition in cell membranes. In this IW, we first discuss the ways different mutations in mice and patients with AD pathology might cause epilepsy in AD. Then we ask if the effects of amyloidogenic APP processing on neuronal excitability is sufficient to explain seizure generation. We also consider the role of Na-channelopathy in seizure generation in mice and patients with AD. Finally, we address the question whether abnormal network re-organization could be the critical factor in seizure generation.

IW.02

COPY NUMBER VARIATION IN THE EPILEPSIES

Sanjay M. Sisodiya[1], Ingrid Scheffer[2], Sarah von Spiczak[3] and Heather Mefford[4] ([1]Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, United Kingdom; [2]University of Melbourne, Melbourne, VIC, Australia; [3]Christian-Albrechts University Kiel and University Medical Center Schleswig-Holstein, Kiel, Germany and [4]University of Washington, Washington, WA)

Summary: Progress in the genetics of the epilepsies continues at a striking pace. Real clinical benefits are being realised for patients, for diagnosis, prognosis and management. Dravet syndrome stands out as a dramatic example of genetic causation providing diagnostic clarity, basic explanation of disease biology and treatment guidance. In common with many other neuropsychiatric diseases, copy number variants (microdeletions and duplications) are emerging as an important category of genetic causation in the epilepsies. Several recurrent microdeletions/duplications have been described, with a larger number of private or unique variants.

Much remains to be done from a genetic perspective in understanding the mechanisms whereby these variants lead to epilepsy phenotypes, especially as the same variant can lead to other neuropsychiatric, or entirely extra-neurological, phenotypes. Many hypotheses have been proposed, including unmasking of recessive alleles, gene interruption, gene fusion, imprinting, alteration of long-range control elements and alteration of chromatin structure/position. Clear explanations have yet to be discovered, though the methods to explore causality and mechanisms are being employed, with the tantalising prospect of the discovery of more 'epilepsy genes' being one reason to pursue basic science research in this area.

From a clinical perspective, more and more copy number changes are likely to be found during routine clinical investigation, as more laboratories move to tools for examination of chromosomal rearrangements that produce high-resolution data on structural genetic variants. Practicing clinicians will therefore find themselves faced with often detailed reports, for example listing variants of 'likely pathological significance', 'no clinical significance' and 'unknown significance'.

This is one area in particular, however, where close collaboration between basic scientists and clinicians will prove informative and productive. Clinicians with access to the patients they are caring for will be able to provide clinical and investigational data from individual patients that inform genetic studies; widely-accessible databases, such as DECIPHER, will allow the sharing of information; geneticists and bioinformaticians will be able to apply burgeoning web resources in detailed dissection of copy number changes. The integration of all these approaches promises to allow us to make the most of these new discoveries, to illuminate our understanding of the epilepsies and hopefully to help improve the lives of people with epilepsy. This translational workshop aims to illustrate these concepts and place copy number change in the broader context of epilepsy genetics.

Sunday, December 5, 2010

Poster Session 2
8:00 a.m.-6:00 p.m.

2.001

HIGH RESOLUTION COPY NUMBER VARIATION OF ION CHANNEL GENES IN EPILEPSY

Alicia M. Goldman[1], T. L. Klassen[1], W. Gu[2], F. Zhang[2], V. Bomben[1], T. T. Chen[1], J. R. Lupski[2] and J. L. Noebels[1,2] ([1]Neurology, Baylor College of Medicine, Houston, TX and [2]Molecular and Human Genetics, Baylor College of Medicine, Houston, TX)

Rationale: Single nucleotide genetic variation is a known source of familial and sporadic disease. Recent evidence shows that the frequency of de novo genomic rearrangements, including copy number variations (CNVs) is about four orders of magnitude greater than the rate of nucleotide-based mutations. The important contribution of CNVs to epilepsy phenotypes is only now being recognized with the application of array based whole genome comparative hybridization (aCGH) platforms. Ion channel genes, despite their relative abundance and critical function in the excitable network, have been underrepresented in whole genome scans. Given the high incidence of Mendelian channel variants in epilepsy, we designed a custom CNV chip targeting this candidate gene superfamily, which represents ~1% of the genome.

Methods: We developed a custom built ion channel gene-specific comparative hybridization array (ICCH array) that interrogates all known exons in 247 human ion channel subunit genes, and used the chip to screen a cohort of 47 patients with idiopathic epilepsy.

Results: We identified 183 duplications affecting 56 channel genes with an average of four duplications per individual, and 169 deletions affecting 30 genes with an average of 3.6 deletions per individual. We observed that chromosomes and genes differed in their likelihood of being affected by CNVs. CNV variation was observed in known human epilepsy genes as well as in ion channel genes previously unlinked to human excitability disorders, thus identifying novel candidate disease genes.

Conclusions: Our targeted gene array project is the first to survey all known ion channel genes at high resolution for structural aberrations with unprecedented sensitivity. With the new platform we can move beyond single nucleotide polymorphisms to study a new dimension of genetic variation contributing to epilepsy. The ICCH array represents an innovative, rapid, and cost effective approach for uncovering novel disease mechanisms from a defined gene set and discovering novel ion channel disease genes.

Supported by NIH (AG, JLN) and Mcknight Brain Disorders Award (JLN).

2.002

EPILEPTOGENIC REGIONS OF HUMAN CORTICAL DYSPLASIA DISPLAY A PERSISTENTLY IMMATURE GABAERGIC PHARMACOLOGIC PROFILE

Laura A. Jansen[1,2], W. H. Roden[1], L. D. Peugh[1], H. K. Alexander[1] and J. G. Ojemann[1,3] ([1]Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA; [2]Pediatric Neurology, University of Washington, Seattle, WA and [3]Neurological Surgery, University of Washington, Seattle, WA)

Rationale: Cortical dysplasia is a common cause of intractable epilepsy in infants and children, producing seizures that are frequently resistant to GABAergic anticonvulsant medications. In this study, we sought to better understand the cellular mechanisms of this resistance through analysis of responses to agents that modulate GABA-A receptor function in resected dysplastic cortex as compared with age-matched control cortex.

Methods: Cortical tissue from children undergoing epilepsy surgery at Seattle Children's Hospital was snap frozen in liquid nitrogen and stored at -80° C. Frozen control neocortical specimens were obtained from the NICHD Brain and Tissue Bank for Developmental Disorders. The membrane fractions of the frozen tissues were injected into Xenopus oocytes, resulting in incorporation of the brain membrane vesicles with their associated receptors into the oocyte cellular membrane, allowing two-electrode voltage clamp analysis of GABA-A receptor currents. An additional membrane fraction was isolated and subjected to Western blot analysis.

Results: Fourteen control and eleven focal cortical dysplasia (FCD) type 2A specimens were analyzed. In the control specimens, maturation of GABA-A receptor pharmacologic properties was noted, as older children (age > 3 yrs) displayed decreased receptor affinity, increased response to the alpha 1 subunit-selective benzodiazepine site agonist zolpidem versus the nonselective benzodiazepine diazepam, and increased degrees of current enhancement by the barbiturate pentobarbital and by the neurosteroid 5á-pregnane-3á-ol-20-one. In contrast, the pharmacologic profiles of the epileptogenic FCD 2A specimens obtained from both infants and older children were most comparable to those seen in immature control cortex. The maturation of GABAergic pharmacologic properties in control children, as well as the dysmaturity present in the FCD 2A specimens, was directly related to the level of GABA-A alpha 1 subunit expression and inversely related to the level of alpha 4 subunit expression.

Conclusions: Epileptogenic regions of focal cortical dysplasia type 2A demonstrate immature responses to GABAergic pharmacologic agents, which may contribute to resistance to current anticonvulsant therapies and suggest alternative treatment approaches.

2.003

DIFFERENTIAL METABOTROPIC GLUTAMATE RECEPTOR TYPE 5 (MGLUR5) EXPRESSION IN THE HIPPOCAMPUS OF PATIENTS WITH MESIAL TEMPORAL LOBE EPILEPSY

Ludmyla Kandratavicius[1,2], P. Rosa-Neto[3], M. R. Monteiro[2], M. C. Guiot[4], C. G. Carlotti Jr[5], J. A. Assirati[5], J. P. Leite[2] and E. Kobayashi[1] ([1]Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, QC, Canada; [2]Neurosciences and Behavior, Ribeirao Preto Medical School, University of Sao Paulo, Ribeirao Preto, Brazil; [3]Neurology and Neurosurgery, Translational Neuroimaging Laboratory, Douglas Research Institute, McGill University, Montreal, QC, Canada; [4]Pathology, Montreal Neurological Institute, McGill University, Montreal, QC, Canada and [5]Surgery, Ribeirao Preto Medical School, University of Sao Paulo, Ribeirao Preto, Brazil)

Rationale: Hippocampal sclerosis is the main pathological substrate in mesial temporal lobe epilepsy (MTLE), and is characterized by neuronal loss, gliosis and axonal reorganization.

mGluR5 is a post-synaptic receptor that modulates glutamatergic neurotransmission. Increased hippocampal mGluR5 protein expression in MTLE has been described in humans and animal models, but PET studies have shown decreased in vivo mGluR5 binding in the epileptogenic hippocampus, suggesting that these receptors might be dysfunctional. Our goal was to analyze the pattern of mGluR5 expression in the hippocampal formation of MTLE patients and to evaluate if mGluR5 expression is associated with changes in neuronal density, mossy fiber sprouting and microtubule-associated protein 2 (MAP2) expression.

Methods: We studied 43 hippocampi from refractory MTLE patients who underwent en bloc resection and 10 control hippocampi from necropsy (no pre-mortem neurological disorders). Formalin fixed and paraffin embedded sections were submitted to immunohistochemistry for NeuN, MAP2, mGluR5 and neo-Timm. Hippocampal subfields were defined according to Lorente de No's classification and quantification of neuronal density was performed according to Abercrombie's method. Positive immunoreactive (IR) area and gray value (GV) were estimated with ImageJ software. Statistical analyses were performed using SPSS 11.

Results: Neuronal loss was identified in most MTLE hippocampal formation subfields, with sparing of subiculum, parasubiculum and entorhinal cortex. Corrected by neuronal density, mGluR5-IR was increased in all subfields (2.5 to 10-fold higher in MTLE, $p<0.02$). MTLE hippocampi showed loss of correlation between CA3 and CA1 mGluR5 and neuronal density, which was strong in control hippocampi ($R=0.98$, $p=0.002$). Correlation between mGluR5-IR and neuronal density in MTLE was seen only at CA4 ($R=0.83$, $p=0.006$).

MTLE MAP2-IR was increased in the granular layer and CA2 ($p<0.003$) and reduced in the other subfields ($p<0.03$) except for the subiculum and entorhinal cortex, where there were no differences with controls. There was a strong correlation between MAP2 and mGluR5 expression in CA3 in MTLE ($R=0.78$, $p=0.01$), but not in control hippocampus. There was a moderate positive correlation between mGluR5-IR in the granular layer and GV of sprouted mossy fibers in the inner molecular layer ($R=0.50$, $p=0.02$) in MTLE.

Conclusions: mGluR5 upregulation in MTLE hippocampi is present in almost all subfields, despite massive neuronal loss in sectors such as CA1 and prosubiculum. A strong positive correlation between mGluR5 and MAP2 was seen only in CA3, suggesting an increase in postsynaptic expression of the receptor in this sector. Loss of correlation between mGluR5 and neuronal density at sectors with cell loss such as CA1, suggests that non-neuronal or outer neuron perycaria elements may contribute to mGluR5 upregulation seen in MTLE hippocampi.

2.004

DIFFERENCES IN PERSISTENT CALCIUM AND SODIUM INWARD CURRENTS BETWEEN FOCAL AND PARAFOCAL REGIONS IN PEDIATRIC NEOCORTICAL EPILEPSY

Charles Marcuccilli[1], M. Király[1], A. K. Tryba[2], S. M. Lew[3] and F. P. Elsen[4] ([1]Neurology, Medical College of Wisconsin, Milwaukee, WI; [2]Physiology, Medical College of Wisconsin, Milwaukee, WI; [3]Surgery, Medical College of Wisconsin, Milwaukee, WI and [4]Seattle Children's Research Institute, Seattle, WA)

Rationale: We have previously demonstrated differences in excitability between focal versus parafocal neocortical tissue obtained from pediatric patients with intractable epilepsy stratified by histology. The purpose of the current study is to determine whether there are corresponding differences in inward voltage-activated currents between focal and parafocal tissue.

Methods: Human neocortical tissue was removed from patients with medically intractable epilepsy and obtained for experimental use with an IRB-approved protocol. EcoG, source localization and clinical relevance determined the sites selected for subsequent *in vitro* electrophysiologic brain- slice studies. In this study, slices for electrophysiological recordings were selected only when clear differences between the epileptic foci (focal tissue) and surrounding area (parafocal tissue) were observed during intracranial EEG monitoring. Upon resection, the tissue was placed into artificial CSF (ACSF). Voltage-clamp recordings of layer V pyramidal neurons were conducted in a 25$^{E\%}$C recording chamber perfused with carbogen-saturated ACSF. The intracellular solution contained TEA and Cs, to block potassium currents. Voltage-activated sodium currents were blocked with either 1 µM TTX or 20 µM riluzole, while calcium currents were blocked with 200 µM $CdCl_2$. Standard voltage step protocols were used.

Results: A total of 36 neocortical neurons from 15 patients were analyzed with 18 neurons each coming from the parafocal versus focal regions. No significant differences in membrane properties between focal and parafocal areas were observed in terms of membrane capacitance, access resistance, or input resistance. However, persistent calcium (I Ca^{2+}P) current densities were significantly higher between -10.0 and +10mV in focal compared to parafocal regions (p=0.026, 0.050 and 0.014, respectively, n=21). No significant differences in transient Ca^{2+} or Na^+ currents were observed between focal or parafocal neurons. Interestingly, persistent Na^+ current (INaP) densities were also significantly enhanced between -40 and -10 mV in parafocal compared to focal regions, in this cohort (p<0.028, n=21).

Conclusions: The present study suggests that there are significant voltage-dependent differences between focal and parafocal areas in neocortical tissue obtained from patients with intractable neocortical epilepsy.

Funding supported by: Advancing Healthier Wisconsin (CJM) and Emory T. Clark Foundation (CJM, AKT).

2.005

IN-SITU SINGLE-UNIT MICROELECTRODE RECORDINGS FROM HYPOTHALAMIC HAMARTOMAS DEMONSTRATE BIMODAL NEURON FIRING RATES

Peter N. Steinmetz[1,2], S. Wait[2], G. P. Lekovic[2], H. L. Rekate[2] and J. F. Kerrigan[1] ([1]Neurology and Comprehensive Epilepsy Center, Barrow Neurological Institute, Phoenix, AZ and [2]Neurosurgery, Barrow Neurological Institute, Phoenix, AZ)

Rationale: Hypothalamic hamartomas (HH) are rare congenital tumors occurring in the ventral hypothalamus. HH are intrinsically epileptogenic, but the basic cellular mechanisms responsible for seizure generation are unknown. Prior studies of surgically-resected HH tissue slices have shown that the small HH neurons possess intrinsic pacemaker-like firing. We sought to determine if such firing is present in situ, prior to the disruption of network connections by resection.

Methods: We recorded extracellular potentials reflecting single neuron activity from bundles of 9 microwires (38 ìm diameter) inserted through a surgical endoscope into the HH prior to resection (Lekovic GP, et al., Neurosurgery, 2009). Extracellular potentials were sampled at 29412 Hz and bandpass filtered (300-3000 Hz). Filter output was examined for single unit spike activity, with analysis of 1.1 millisecond (ms) epochs surrounding the time of voltage extrema (>2.8 channel s.d.). These were isolated and sorted into spike clusters of similar waveform shape using a Classification Expectation-Maximization (CEM) clustering algorithm.

Results: We recorded in situ single unit activity from 11 patients (mean age 14.6 years ,range 2.2-34.1 years; 7 females, 64%), under anesthesia with sevoflurane. In total we recorded spontaneous firing from 222 neurons. The mean firing rates of these neurons segregated into two groups (figure 1), one with a low firing rate (FR) of 1.3 spikes/second, and a second group with a higher FR of 15.2 spike/second (Hartigan-Hartigan dip test for more than one mode, p<0.00001). The burst ratio (BR = fraction of inter-spike intervals < 10 ms divided by fraction of inter-spike intervals > 10 ms) also showed a strongly bimodal distribution (mode 1 = 0.022, mode 2 = 0.18; p<0.00001).

Conclusions: These results demonstrate that in situ spontaneous firing rates of HH neurons (under conditions of anesthesia with halogenated gases) segregate into two groups. The higher firing rate observed here is similar to firing rates previously reported for small HH neurons in acutely dissociated single-cell preparations (10.5 +/- 0.8 Hz) (Wu J, et al., Ann Neurol, 2005) and freshly-resected HH tissue slices (6.6 +/- 1.0 Hz) (Kim DY, et al., Epilepsia, 2008). A subgroup of HH neurons fire spontaneously even when all network connections are preserved in the intact brain.

IMAGE: images/905988_A.jpg

2.006

INCREASED EXPRESSION OF GROWTH ASSOCIATED PROTEIN 43 (GAP-43) IN HUMAN EPILEPTIC DYSPLASTIC CORTEX

Zhong Ying, R. O'Dwyer, J. Gonzalez-Martinez, W. Bingaman and I. Najm (Epilepsy Center, The Cleveland Clinic, Cleveland, OH)

Rationale: Growth associated protein 43 (GAP-43) is a neuronal presynaptic membrane-bound protein that has been shown to play critical roles in the formation of neuronal synapses and establishment neural circuitry in developmental brain, axonal sprouting and regeneration after injury in adult peripheral nervous system, and long term potentiation and modulating neurotransmtter release in mature brain. GAP-43 is expressed at high levels during development and regenerations and there is a sharp decline in GAP-43 level once synaptogenesis is complete. Cortical dysplasias (CDs), a neuronal migration disorder, are a prominent cause of medically intractable epilepsy. To explore abnormal synaptic formation and neuronal

membrane remodeling in CDs, we investigated the pattern and level of GAP-43 expression in human epileptogenic dysplastic cortex in brain specimens surgically resected from 10 patients with medically intractable focal epilepsy due to CDs.

Methods: We used immunohistochemical (IHC) staining to examine the cellular expression patterns of GAP-43 protein in dysplastic cortex and normal appearing cortex in 7 patients, and western blot techniques to quantify the GAP-43 protein level in 5 patients. For western blot study, the resected cortical tissues from each patient were grouped into epileptic and nonepileptic, as determined by prolonged subdural electrode recording or direct intraoperative electrocorticographic recording. The tissues from 2 patients were performed for both IHC staining and western blot analysis.

Results: In all 7 patients that GAP-43 IHC was performed, GAP-43 stained neuropils (the tubular structures) were increased in the dysplastic gray matter as compared with the normal appearing cortex. The GAP-43 protein levels as determined by western blot were increased in the epileptic cortex as compared with nonepileptic cortex.

Conclusions: Our current study by both immunohistochemistry and western blot is the first to show an increase in the GAP-43 protein in epileptic dysplastic cortex resected from patients with focal CDs.

The increased GAP-43 proteins in the dysplastic regions as identified by IHC likely localized in the axonal terminals. The heavily GAP-43 stained tubular structures may also represent the myelin forming oligodentrocytes wrapped around the aberrant formed axons. These need to be confirmed by double labeling of GAP43 with neurofilament protein and myelin basic proteins in the future.

These results suggest that GAP-43 associated abnormal axonal formation may underline on the cellular mechanisms that contribute to the altered neuronal communication which may mediated hypersynchronization of neuronal activity leading to seizure generation in focal cortical dysplasia

2.007

NEURONAL BINUCLEATION AND CYCLIN EXPRESSION IN HUMAN TEMPORAL LOBE EPILEPSY

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Rationale: There is a growing interest to the mechanisms of seizure-induced neuronal injury in the human brain. Several studies report markers of neuronal death found in temporal lobes specimens removed surgically for intractable temporal lobe epilepsy (TLE). (Henshall et al., Neurology 2000; 55: 250-257; Yamamoto et al., J Neuropathol Exp Neurol 2006; 65: 217-225). The presence of the high nuclear expression of cyclin B (an enzyme specific for the G2 phase of the cell cycle) accompanied by neuronal cytoplasmic expression of the death-related Bax protein in the hippocampus of patients with epilepsy has been demonstrated (Nagy, Esiri, Exp Neurol 1998; 150:240-247) and interpreted as evidence of cell cycle disturbances associated with hippocampal neuronal cell death in TLE. However, further evidence of cell cycle disturbances is needed and the mechanisms still remain obscure.

Methods: We evaluated neuronal expression of cell cycle proteins in 20 adult patients with chronic TLE undergoing temporal lobe surgery for seizure control. Surgically resected hippocampal specimens were fixed for pathomorphological/immunohistochemical analysis or frozen for biochemical analysis. Fixed samples were then stained for Nissl or cell cycle components. In frozen samples, cell cycle proteins were assayed using Western blots.

Results: In hippocampal specimens we found neuronal expression of G2 cell cycle phase proteins (cyclin B1 and Cdc2), as well as PCNA. Western blots also revealed the expression of cell cycle proteins, including those of late phases. Most interesting, an appearance of binucleated neurons was revealed in many Nissl stained samples. Binucleated neurons looked degenerating or otherwise normal, some of them were PCNA-positive

Conclusions: These results are the first evidence for neuronal binucleation in hippocampus of patients with chronic pharmacoresistant TLE and confirm the involvement of aberrant cell cycle in neuronal cell death in epilepsy.

2.008

HIGH GM-CSF CONCENTRATIONS IN POST ICTAL PLASMA: A POSSIBLE TEMPORAL LOBE SEIZURE BIOMARKER

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Rationale: Inflammatory pathways are activated by seizures leading to production of the proinflammatory cytokines. For example, interleukin(IL)-1â has been shown to be synthesized in glia in response to proconvulsants. However, IL-1â levels are unlikely to be good biomarkers of seizures because reliably high cerebrospinal fluid concentrations from epilepsy patients have not been found. In somatic tissue, IL-1â induces an increase in GM-CSF granulocyte-macrophage colony-stimulating factor (GM-CSF) synthesis. There are published articles identifying brief peripheral elevation in other inflammatory cytokines such as IL6 in post ictal patients. A dependable plasma biomarker for seizures is yet to be discovered. We included GM-CSF in a global search for potential ictal biomarkers using peri-ictal plasma sampling of inflammatory cytokines. To mirror previous studies subjects were selected for likely temporal lobe seizures.

Methods: Plasma samples were obtained from subjects in the epilepsy monitoring unit for routine care (prior to seizures through up to 37 hours post ictal.) Sodium citrate stabilized plasma was collected, immediately put on ice, and then spun in a cold centrifuge. Immediately after centrifugation, the samples were stored at -80 degrees C. The samples were then assayed using a multiplexed ELISA platform (meso scale, Gaithersburg, MD) and compared to historical normal controls. There were seven samples from 5 unique temporal lobe epilepsy subjects.

Results: In this pioneer experiment, the ratio of plasma GM-CSF levels to the average of the control patients showed consistent marked elevation in concentration of 4 of 5 temporal lobe epilepsy patients.

The average ratio of subject to control for these four was 3.6. In these subjects, the average GM-CSF concentration in pg/ml was 1.46 +/- 0.16 [SD], 95% CI [1.30-1.63] compared to control 0.76+/- 0.19 [SD], 95% CI [0.61-0.91] p<0.0002. One temporal lobe epilepsy patient had a substantially low ratio of -2.7. A syncope subject had a ratio similar to that of the historical controls. The IL-6 levels and IL-1â were similar to controls in most cases.

Conclusions: In four out of five temporal lobe epilepsy patients, plasma concentrations of GM-CSF were markedly elevated compared to controls. The last temporal lobe epilepsy subject had a very low ratio. IL-1â levels were not as consistent as predicted from previous literature. IL-6 levels were not as consistent, likely because of the small sample size and sampling times outside the optimal time window. Only GM-CSF showed characteristics that indicate it could be a good biomarker for frequency of temporal lobe seizures. A prominent potential confounder is that the origin of the GM-CSF is unknown. It could be peripheral, or it could have leaked from the CSF though compromise of the blood brain barrier during a seizure.

IMAGE: tables/905948_T1.jpg

2.009

EFFECT OF EVEROLIMUS ON NORMAL-APPEARING WHITE MATTER IN PATIENTS WITH TUBEROUS SCLEROSIS (TS)

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Rationale: TS is a potentially devastating disorder caused by mutations in *TSC1* or *TSC2* that result in constitutive mTOR activation. Lesions in the brain include subependymal giant-cell astrocytomas (SEGAs) and neuronal tubers, epileptogenic cerebral cortex abnormalities. Recently, an open-label, phase II trial (NCT00411619) of everolimus, an orally bioavailable selective mTOR inhibitor, demonstrated a significant reduction in SEGA and tuber volume and a decreased frequency of seizures. This subgroup analysis investigated potential changes in the normal-appearing white matter in patients from this study.

Methods: Patients aged e"3 years with a definitive TS diagnosis and evidence of serial SEGA growth (on MRI) were treated with everolimus 3 mg/m^2/d orally (titrated to tolerability to achieve target trough concentrations of 5-15 ng/mL). MRI scans were performed at baseline and at 3, 6, and 12 months. For this subanalysis, we reviewed patients who received DTI as part of their imaging protocol. DTI imaging (15 directions, 1.5 Tesla [GE], 3×3×3 mm, interpolated to 1.5×1.5×3 mm) was used to calculate fractional anisotropy (FA) and axial, radial, and mean diffusivity within regions of interest in the normal-appearing white matter. Treatment effect was measured by comparing these data from patients after 12-18 months of treatment to baseline imaging, using a paired t-test.

Results: Twenty-eight patients were enrolled; median duration of treatment was 21.5 months (range, 4.7-34.4). Twenty subjects had sufficient DTI data at multiple time points, including 17 subjects with baseline DTI imaging and 3 subjects with first DTI imaging at 3 months into treatment. Comparing these baseline values to 12-18 months after the treatment, a significant change in the FA was observed in this group in the corpus callosum, internal capsule, and inferior longitudinal fasciculus (all $p < 0.05$). Median change in FA was 0.05 and was mainly driven by a significant decrease in radial diffusivity in all 3 areas; no significant changes in mean and axial diffusivity were observed.

Conclusions: A significant change in FA and radial diffusivity was observed in patients with TS treated with everolimus. These findings support improvement in structural integrity of the measured white matter tracts after treatment with everolimus. As radial diffusivity has been associated with myelin integrity, these changes could represent improvements in myelination. Alternatively, everolimus may decrease abnormal cells in the white matter resulting in a more uniform directional organization of neurons within these tracts. This improvement in white matter integrity may be partly responsible for observed improvements in seizure frequency with everolimus in this population. These findings raise the possibility that the genetic defect of TS in the brain may be modified, even in radiographically normal-appearing white matter.

2.010

HUMAN HERPESVIRUS-6 (HHV6) AND CHILDREN WITH MEDICALLY REFRACTORY EPILEPSY

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Rationale: HHV6 had been detected in brain specimens removed from adult patients with mesial temporal lobe epilepsy (MTLE). It is unclear whether HHV-6 plays role in children with temporal lobe epilepsy.

Methods: All brain specimens resected from children with medically refractory epilepsy who underwent epilepsy surgery between 4/2009-3/2010 at Children's Hospital of Alabama were tested by PCR for HHV6 DNA.

Results: 37 children underwent resective epilepsy surgery. 27 brain specimens were available for HHV6 analysis (mean age of seizure-onset 3.5 yrs, mean age of operation 8.5 yrs). Only 3 patients had temporal lobe epilepsy (TLE), 2 of which had abnormal MRI consistent with MTLE. 24 patients had extratemporal epilepsy: 3 tuberous sclerosis, 1 Sturge-Weber syndrome, 1 Rassmussen's encephalitis, and 19 focal cortical dysplasia. Only the brain specimen from a patient with Rasmussen's encephalitis was positive for HHV6 DNA, and all other specimens, including cases with TLE, were negative for HHV6 DNA.

Conclusions: These results do not support a role for HHV6 in pediatric TLE, although the small sample size studied does not eliminate an association. The presence of HHV6 in a patient with Rasmussen's encephalitis raises the possibility of HHV6 association in Rasmussen's encephalitis pathogenesis.

2.011

EPILEPSY SELF-MANAGEMENT IN OLDER ADULTS: A PILOT STUDY

Wendy Miller and J. M. Buelow (School of Nursing, Indiana University, Indianapolis, IN)

Rationale: In the United States (US), those aged 60 years and older are widely affected by epilepsy. Thus, yearly, thousands of older adults begin self-managing this complex condition. Despite the high incidence of epilepsy in older adults and knowledge that epilepsy self-management (ESM) affects important outcomes, researchers have not

investigated the ESM experiences of older adults. While knowledge of the ESM experiences of younger adults exists, this research may not be applicable to older adults with epilepsy given the uniqueness of this population in terms of co-morbidities, physiologic changes, and polypharmacy. Understanding the impact of epilepsy on the lives of older adults, as well as the challenges they face in managing the disease, is necessary to develop effective interventions to improve ESM for this population. Thus, the purpose of this pilot study was to describe the ESM experiences of older adults diagnosed with the disease at age 60 or older.

Methods: A qualitative descriptive design was employed. Five older adults (mean age 68 years; mean time since diagnosis 3.5 years) were interviewed to generate the data set. Interview questions were intended to elicit respondents' experiences with ESM, including how their lives have changed since epilepsy diagnosis, challenges encountered in managing the disease, management strategies used, and the overall effect of the disease on daily functioning. Data were analyzed via content analysis techniques. Reoccurring themes were identified.

Results: Three main themes, *Perceived Life Changes since Diagnosis, Challenges*, and *Types of ESM Strategies* (See Table and Figure 1), comprised of sub-themes, emerged. Respondents reported marked and mostly undesirable changes in their lives since being diagnosed, including lifestyle changes, changes in perceived well-being, and physical and emotional changes in the form of unpleasant symptoms. Respondents also reported challenges associated with managing epilepsy, including difficulties in receiving a correct diagnosis, receiving inadequate education at the time of diagnosis and feeling unprepared for the seriousness of the disease, problems maintaining pre-diagnosis levels of independence, and difficulties involving medications. The use of two types of ESM strategies—those aimed at managing the disease itself and those aimed at managing the life changes and challenges associated with having epilepsy—were reported. Further, strategies can be categorized as proactive or reactive.

Conclusions: The present findings reveal that adults diagnosed with epilepsy late in life have some ESM experiences/needs and are at risk for certain undesirable life changes and management challenges that are not found in the younger adult ESM literature. General ESM interventions based on younger adult research may not be as effective in older adults, and thus must be tailored to meet their unique needs. To inform the development of such interventions, more explanatory and interpretive qualitative research with this population is needed, and the results of this study can be used to guide and inform the design and research questions of future larger-scale studies.

Description of Major Themes and Sub-Themes

IMAGE: tables/906762_T1.jpg

*Types of ESM strategies are overlapping and not mutually exclusive. For example, a strategy could be both disease/treatment-focused and proactive in nature.

IMAGE: images/906762_A.jpg

2.012

CAREGIVER ANXIETY ASSOCIATED WITH THE INPATIENT PEDIATRIC EPILEPSY MONITORING EXPERIENCE

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Rationale: To investigate the prevalence and factors that lead to caregiver anxiety associated with admission to the Pediatric Epilepsy Monitoring Unit (PEMU) in order to improve preadmission education.

Methods: A prospective study of all patients admitted to the PEMU at our pediatric epilepsy center over a 9 mos period, using a deindentified questionnaire developed for the purpose of this study. The questionnaire focused on both preadmission and inpatient nursing and physician communication about both the technical aspects of the monitoring and their child's condition. The questionnaire had both a fixed and free response section. Institutional IRB approval was obtained.

Results: During the testing period, 249 patients were admitted to the PEMU and provided the questionnaire. The age range was <1 to 21 years of age (mean 9 yrs); 114(46%)were males, and 135(54%) were females. We had 100(43%)responders. Of these, 40% had epilepsy, and 81% were monitored for 1-3 days(mean 2.8 days). 56% had other neurological conditions, and 54% had other chronic medical conditions. 88% had previous EEG experience. 55% had a decrease in their anti-epileptic drugs (AEDs) while admitted, and 68% were discharged on more AEDs.

68% of the caregivers identified a degree of anxiety, and 17% identified themselves as "very anxious." 46% of responders felt they were not optimally prepared, and identified this as a cause of anxiety. For 38%, not having a seizure during monitoring was identified as a source of anxiety. 32% identified either staying in the hospital or being away from home as the cause of their anxiety. Caregivers felt that nursing and physican communication was comparable: 93% and 86%, respectively. From the free response section of the questionaire, identified areas of improvement include: improved accomodation for children with autism spectrum disorders(12%), improved preadmission education and expectations of the stay, and clarification of caregiver role during the monitoring.

Conclusions: We have identified the prevalence of anxiety associated with the PEMU experience as well as causative factors. We plan to reexamine patients after undertaking steps to improve the preadmission communication between nursing and families, partner more closely with child life, and focus on care of patients with autism spectrum disorder. Successful interventions can not only serve as models for other PEMU centers, but form common goals for quality improvement in a network of pediatric epilespy centers.

2.013

MANAGING AGGRESSION IN AN EPILEPSY MONITORING UNIT(EMU): A CASE OF ICTAL RAGE

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Rationale: The association between violence and epilepsy has been much debated in the literature. Aggressive behaviour related to seizures can be ictal, post ictal or inter ictal. Ictal violence is extremely uncommon with only rare cases documented in the literature (Delgado-Escueta et al 2002).These involved spontaneous non-directed stereotyped aggressive movements with violence that was resistive rather than directed. Resistive violence refers to unintended aggression towards others that occurs when someone attempts to restrain or assist a patient during a seizure. Post ictal aggression is often associated with confusion or psychosis and the episodes last longer than ictal violence. There is evidence that temporal lobe discharges which involve the hippocampus, amygdala and hypothalamus particularly involving the

left hemisphere as well as specific frontal regions are likely to lead to episodes of violent behaviour (Fenwick,1986; Marsh and Krauss,2000). In Campbell's ongoing study (2009) on workplace violence 89% of physical aggression is patient related.We will present a case report of a patient exhibiting ictal rage as documented by video EEG which resulted in staff injury. Strategies for preventing and managing workplace violence as it pertains to this patient population will be reviewed.

Methods: -Literature review of the neurobiology of aggression and patient related violence

-retrospective review of incidents of aggression over the last 5 years in the EMU of our institution

-case review of ictal rage

Results: 13 incidents of aggression in 8 patients/ 1212 admissions in the past 5 years.

Ictal: (1) A male patient with ictal rage had bitemporal independent inter-ictal discharges and seizures arising from the left temporal lobe. MRI showed abnormal left hippocampus and neuropsychology pointed to left hemisphere abnormalities. (Case Presentation)

Post ictal:There were 4 events(3 male)following secondary generalized seizures:2 left hemisphere, 1 bitemporal and one right occipital.

Inter ictal: There were 8 events (2 male and 2 female): 4 events in 1 female patient with severe behavior disturbances as a result of viral encephalitis, 2 events in intellectually delayed male post right temporal resection and occipital focus,1 male left temporal focus and psychiatric co morbidity, and 1 female with intellectual delay but no apparent epilepsy.

Recommendations were made for improving patient and workplace safety. The event of ictal rage precipitated a review of the risks associated with the EMU patients. Senior administration, occupational health and safety, and unit leadership analyzed the situation using root cause analysis. Modifications to the environment and staffing quotas ensued.

Conclusions: Ictal rage is a rare occurrence, 1% of admissions over 5 years. Its prediction and management is essential to provide a safe environment for patients and staff. Debriefing of this rare event using a root cause analysis model resulted in system changes. Use of telemetry monitoring and staff expertise are critical in managing peri ictal and ictal violence.

2.014

THE ROCKY ROAD TO EPILEPSY SURGERY: A CASE STUDY

Lisa Ortiz and C. Bordson (Barrow Neurological Institute, Phoenix, AZ)

Rationale: Patients with localization related epilepsy who continue to have seizures after failure of multiple anti-epileptic medications are said to have refractory epilepsy. Approximately twenty to thirty percent of all epilepsy patients have medically refractory seizures.

Methods: This poster will present a case study of a 29-year-old male with refractory epilepsy who underwent multiple epilepsy surgeries. Each step of his diagnostic process and surgical experience will be discussed, including scalp electrodes, depth wires, subdural grid placement, and finally an Anterior Temporal Lobectomy.

Results: Diagnosis, nursing care, post-operative complications, particularly the development of bilateral epidural hematomas, and patient outcomes will be discussed in this poster presentation.

Conclusions: Surgical evaluation is appropriate for patients with seizures thought to be focal in origin, those who are medically refractory, and whose quality of life are significantly impaired by their seizures. Passionate, highly trained Epilepsy Monitoring Nurses play an invaluable role in the diagnosis and treatment of these patients.

2.015

MAKING MEANING OF LIFE WITH EPILEPSY: THE USE OF METAPHOR IN UNDERSTANDING INDIVIDUAL EXPERIENCES

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Rationale: Epilepsy is a particularly disruptive illness as individuals experience increased vulnerability and loss of control due to unpredictable seizures. These events leave the individuals struggling to make sense of their experience in order to regain control of their lives. Metaphor is used to convey how people make sense of a phenomenon such as illness, and this tool can be particularly useful in conceptualizing and communicating one's experience. Understanding the way in which People with Epilepsy (PWE) conceptualize their chronic illness is key to addressing psychosocial health and coping strategies. The current study sought an understanding of epilepsy metaphors as a novel strategy to address the psychosocial needs of PWE.

Methods: A qualitative analysis of published epilepsy narratives (autobiographies and biographies) was conducted. Ten narratives were reviewed, four were written by family members and six by PWE. All accounts were analyzed to identify central metaphors used to describe the experience of epilepsy as a whole, as well as metaphors describing specific aspects of the experience.

Results: Analysis revealed that metaphors play a central role in facilitating one's ability to communicate the experience of epilepsy. While all narratives had been published in the past 10 years, half recounted epilepsy diagnosis and treatment that occurred over 30 years ago. Improved understanding of epilepsy has been accompanied by changes in societal metaphor use, from the earliest references of "demonic possession" to current concepts of "treatable electrical disturbances." Nonetheless, two accounts made reference to epilepsy as "possession" by "evil forces." Most sources identified attempts to find a diagnosis as a "quest." Individuals referred to medical treatment for epilepsy as "being held captive" and "zombie-like." The most recent accounts identified treatment as "freedom" or the self "being under control." The majority of accounts suggested that PWE feel stigmatized by a permanent "stain," "bruise," or other divergence from the perceived norm. The ten accounts analyzed reflected a common narrative structure based on the course of medical treatment, as well as the use of metaphors prevalent in societal discourse on epilepsy.

Conclusions: The current study provides insight into narratives and metaphors that PWE use to make sense of their illness. The observed trends emphasize the central role that both medicalized and socialized concepts play in shaping the individuals' concepts of epilepsy. This research is part of a larger project that seeks to identify medical and cultural epilepsy metaphors that contribute to perceived stigma, in

contrast to those perceived to promote psychosocial health. Future research is hoped to improve communication between PWE and healthcare professionals, ultimately supporting patients' psychosocial adjustment to their condition.

2.016

RECESSION ESCALATES NEED FOR PATIENT SUPPORTS

Ann Marie Bezuyen (Northeast Regional Epilepsy Group Epilepsy Life Links, Middletown, NY)

Rationale: The patient advocacy arm of the Northeast Regional Epilepsy Group (NEREG) of epileptologists, neuropsychologists, nurse practitioners, researchers, dieticians and a comprehensive EEG department was established three years ago. The initial goal of the practice was to create a unique in-house system of treating the whole patient by offering supports outside of the clinical arena that included community and individual epilepsy education, systems advocacy, employment interventions and support groups. A slow start was followed by a sharp increase in patients reaching out for help as they were unable to find services elsewhere. Many of the familiar service agencies lost program funding, were forced to deplete their workforce, or excluded epilepsy patients based on funding structure and acceptance criteria.

Methods: Patient advocacy requests and outcomes were maintained from 2007 through 2009 in an effort to track specific patient life issues that required intervention. The purpose here was to determine the essential functions of the NEREG advocacy program and the need to modify or augment specific interventions.

Results: This three-year retrospective yielded surprising statistics, with 2009 showing a significant rise in requests by NEREG patients. Outreach for assistance increased: 2007(190); 2008 (212); 2009 (1,094). Identified patient issues remained consistent, with a dramatic increase in the number of patients seeking support: Benefit issues: 2007 (99), 2008 (79), 2009 (281). Driving Issues: 2007 (35), 2008 (35), 2009 (130). Employment Issues: 2007 (81), 2008 (81), and 2009 (137). Epilepsy Education: 2007 (33), 2008 (33), and 2009 (163). Mental Health Issues: 2007 (21), 2008 (21), and 2009 (71). Personal Issues: 2007 (1), 2008 (11), and 2009 (46). Recreation Issues: 2007 (0), 2008 (1), and 2009 (15). School Issues: 2007 (37), 2008 (37), and 2009 (136). Support Groups: 2007 (23), 2008 (41), and 2009 (93). Transportation Issues: 2007 (0), 2008 (4), and 2009 (22).

Conclusions: A significant spike in the total number of service requests appeared in 2009, with patients struggling in all areas of life. Benefit acquisition showed the most substantial rise. Patients wrestled with attaining Social Security Insurance, Social Security Disability Insurance, Medicaid, Medicare, housing subsidies, in attaining affordable medications, and in affording medical insurance and/or the increased co-payments for service. This study in services to epilepsy patients highlights the need for acceptance of this advocacy model by other institutions. The positive outcomes patients experience lend to excellence in patient care.

2.017

MANAGING EPILEPSY: PERSPECTIVES OF PROFESSIONALS WITH AND WITHOUT EPILEPSY

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Rationale: Effective management of epilepsy requires partnership between the patient and professionals who support their management efforts. This study involved health care providers with and without experience living with epilepsy and elicited their perspectives regarding challenges facing patients with the condition.

Methods: 101 clinical, academic, and human services thought leaders providing care to people with epilepsy were interviewed by telephone. Interviews comprised twenty questions regarding significant challenges people with epilepsy face in managing their condition. Interviews were audio recorded, transcribed, and coded into thematic groups using an iterative process within NVivo 8. Prevalent themes were examined using a chi-squared test of homogeneity to compare proportions of respondents by profession type and personal experience with epilepsy.

Results: Respondents were clinicians (41%), social service providers (41%), researchers (16%), other (3%). One-third of respondents (n=34) have epilepsy themselves or have a close family member with the condition. Researchers (88%) and social service professionals (56%) saw access to and quality of clinical care as the most daunting factor facing epilepsy patients. Clinicians reported less often that this was the greatest management challenge (22%, $p<0.0001$) and clinicians most often cited psychological effects associated with the condition (32%) as the most important problem. Affording medicines was not seen as a great challenge by most clinicians or researchers, but was by a quarter of social service professionals (27%, $p<0.018$). Virtually no person with personal experience with epilepsy (3%) saw stigma and lack of public understanding as a great challenge to people with the condition although over a quarter (27%) of the respondents without personal experience said this was a great challenge ($p<0.0057$). Respondents with personal experience with epilepsy were much more likely to report that affording medicines was a challenge (27%, $p<0.0625$), and for them, cognitive difficulties were considered a challenge (17%).

When asked about the most important thing a person with epilepsy needs to be able to do to manage the disorder, responses differed by profession type for only one response: medication compliance. Medication compliance was the most frequently mentioned response from clinicians, compared to other professionals ($p<0.05$). Researchers and social service providers most frequently cited the need to understand their own condition as the most important. Responses did not vary significantly by whether the respondent had personal experience with epilepsy.

Conclusions: Professionals need to recognize that their perspectives may be influenced by their disciplinary orientation and personal experience. Services and programs that accommodate different perspectives and are based on a broader picture of epilepsy control may provide more assistance for people trying to manage the condition.

2.018

FOUNDATIONS FOR DEVELOPING A SUPPORT GROUP FOR PARENTS OF CHILDREN WITH INTRACTABLE EPILEPSY: A QUALITATIVE EXPLORATION OF PARENTS' SUPPORT NEEDS

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Rationale: Parents of children with intractable epilepsy face significant caregiver burden. The purpose of this project was to assess parents' support needs and views on support groups for parents of children with epilepsy, in order to help develop a professionally-lead Parent

Support Group (PSG) aimed at improving parent quality of life and reducing caregiver burden.

Methods: Parents were recruited by identifying children diagnosed with intractable epilepsy and followed at the Alberta Children's Hospital. Neurology Clinic staff invited parents to participate in one of two focus groups, offering a neutral environment for discussion and facilitated by a third party (hospital consultant Information and Evaluation Unit). Parents were asked to complete an Informed Consent Form, a Demographic Information Form, and specific questions regarding the logistics of a PSG. The pediatric epilepsy team developed a question guide for the focus group, addressing the following: (a) challenges faced by parents and their individual needs; (b) barriers to and benefits of attending a support group; (c) broad support needs beyond a support group. Focus groups were audio-recorded, transcribed, and analyzed by the third party using thematic analysis.

Results: Eighteen parents, three of which were couples (i.e., 15 total family participants), attended focus groups. Most participants were married (93.3%) women (83.3%) who were in their 30's (mean age = 37.8 years), well-educated (mean years of education = 15.5), and employed (66.6%). The majority of their children with epilepsy (mean age = 7.5 years) had developmental delay (93.3%) with daily seizures (46.6%) and an average of 2.5 antiepileptic medications per child. Thirty-three percent of children had surgical intervention for epilepsy. Theme analysis identified three pervasive themes and associated sub-themes: 1. Relationship Difficulties (Intra-family Responsibilities, Marital Concerns, and Social Isolation Issues); 2. Support System Needs (Talking to Others who Understand, Ability to Learn New Information, and Venting about Troubles); and 3. Health Care System Related Issues (Physician-Related Concerns, Service-Related Problems, and a General Lack of Information). Although parents recognized value in attending a PSG, potential barriers included childcare difficulties, the precarious status of their child's health, and difficulty prioritizing their own needs over those of the family.

Conclusions: Parents of children with intractable epilepsy identified broad concerns, highlighting relationship issues, complex demands of parenting, and support requirements. Parents reported that their primary concern is their child's health, and a PSG will not meet all of their needs. Addressing health-care system issues was identified as a crucial factor in supporting families. This information will be used towards improving program-based systems and developing a PSG model that accounts for potential barriers to participation identified by parents.

2.019

OPINION SURVEY OF HEALTH CARE PROVIDERS TOWARDS PSYCHOGENIC NON EPILEPTIC SEIZURES

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Rationale: Psychogenic non epileptic seizures (PNES) are challenging conditions to diagnose and manage. The opinion of the health care provider (HCP) towards the patients and the disease is of paramount importance and several lacunae remain to be stressed. Amongst HCP, opinion of nurses has not been adequately explored. We attempted to identify areas which need more emphasis to provide optimal care to the patients.

Methods: We approached physicians (attending and resident) of primary care, neurology, psychiatry and licensed nurses regularly taking care of patients of PNES. An anonymous questionnaire (Table 1) was provided to the respondents to be filled out.

Results: Net 124 respondents responded to our survey. Sixty (48.3%) were from primary care, 12.9% from neurology and 7.2% from psychiatry. Thirty-nine (31.4%) respondents were practicing nurses. Amongst physicians 68.2% were resident physicians.

"Non epileptic seizures" was by 35.7% (39/109) as a diagnostic term as against "pseudo-seizure" (22.9%), "stress related seizures" (18.3%), "psychogenic seizures" (13.7%), "functional" and "fake" seizures (4.5% each).

On a numerical scale of 0-10 neurologists reported highest average level of confidence in managing patients of PNES (7.58) followed by nurses (7.15)

Majority (60.1%; 62/103) believed that patients have no control over the spells and they are involuntary.

Amongst 106 respondents, 69 (65 %) opined that video EEG should always be used in making a diagnosis of PNES.

While 66.3% (71/107) respondents would agree with the diagnosis of PNES by an epileptologist, 27.1% would decide on a case to case basis and only 6.5% would disagree.

Psychiatry was felt the best specialty to manage patients after diagnosis (36.4%) followed by neurology (28.4%), psychology (22%) and primary care (12.7%). These responses were not mutually exclusive.

Of 102 respondents, 71.5% would not adjust AED after an increase in spell frequency. 56% (9) neurologists expressed that they may adjust AED before an epileptologist's evaluation.

Only 14% (15/107) felt that the patients be allowed to drive in wake of continuing episodes while the rest either would not support driving (45.7%) or decide on a case-to-case basis (40.1%).

Conclusions: Several important aspects of HCP's opinion towards PNES are revealed. The age old term "pseudo-seizure" seems to have lost favor. Neurologists and nurses have among the highest level of confidence in managing patients of PNES. Interestingly, more than a third of respondents felt that patients of PNES have voluntary control over their episode. Amongst HCP highest percentage of nurses would agree with the diagnosis of PNES by an epileptologist. While majority of responders would not adjust AED before evaluation by an epileptologist, more than half of the neurologists would. A multi-specialty approach to the management of PNES seems to be the most preferred methodology with maximum participation by psychiatrist, neurologist and psychologist. Importantly, only minority (<15%) would allow unrestricted driving in patients with continuing episodes.

Table 1: Survey questionnaire with itemized responses

IMAGE: tables/903672_T1.jpg

Total number of respondents was 124. As not all questions were answered by every respondent, the number of responses per question may not be 124.

2.020

THERAPEUTICS APPROACHES TO THE TREATMENT OF EPILEPSY IN SLOVAKIA

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Rationale: Recognize the doctors' treatment habits. Map the general therapies for the treatment of epilepsy. Identify the proportion of patients with epilepsy at Slovak clinics.

Methods: Methodology: Quantitative questionnaire

Sample Size: 125 respondents (Neurologists)

Location: Slovak Republic

Target Group: Neurologists

Survey Data Collection: 2008

Survey Data Evaluation: September 2009 - October 2009

Results: The patients with epilepsy in Slovakia are treated solely by neurologists. On average one neurologist examines 29 epilepsy outpatients per month. Most of the neurologists (83%) examine less than 5 patients with epilepsy per day.

Total of 50% of neurologists need 30 - 40 minutes to execute the initial examination of an epilepsy patient. To do the same, 32 % of neurologists need 20 - 30 minutes and 18% of neurologists require more than 40 minutes. An ordinary medical visit to the neurologist takes 10 - 20 minutes in 62 % of the cases, 30% of such visits last for 20 - 30 minutes and 4 % of the visits take more than 30 minutes.

Neurologists consider low drug compliance to be caused by the large scale of medication (54%). An epilepsy patient takes 1.6 anti-epileptic drugs (AED) in an average. Low compliance is also caused by the indiscipline of the patients (46%) and a complicated drug dosage (43%).

Neurologists value AEDs mainly for their curative effect, good drug tolerance and minimal side effects. The doctors associate the state without epileptic seizures mostly with valproate (42%) and levetiracetam (25%).

The first choice drug used to treat primary generalized seizures (79%) and juvenile myoclonic epilepsy (JME) (50%) is valproate. In 70% of the cases of partial seizures the doctors use carbamazepine as the first choice. Levetiracetam is the most used from the new generation AEDs to treat partial seizures and JME.

When evaluating AEDs', pregabaline is considered to be inefficient (74%), lamotrigine has a complicated dosage (59%) and topiramate has an unfavorable side-effect profile (56%). zonisamide has an inconvenient price and is the least known among neurologists.

Neurologists proceed differently in case the treatment doesn't result in improvement. Some of them supplement the first choice medication with the new generation AEDs (1/3), others (1/3) are adding a medication with a different curative mechanism. One quarter of neurologists have their own trusted scheme.

Neurologists refrain from adding a medication with the same mechanism (3%) and solely send their patient to other clinic with a higher level of expertise (1%).

When considering the medication, price and the producer of the drug are considered as the least important factors for neurologists.

Conclusions: Therapeutic habits and routine practices in treatment of the epilepsy of the neurologists in Slovak Republic correspond to standard therapeutic algorithms.

2.021

TEACHERS' EPILEPSY KNOWLEDGE AND CONFIDENCE IN INSTRUCTING STUDENTS WITH EPILEPSY: PRELIMINARY FINDINGS

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Rationale: Knowledgeable and confident teachers promote school success for students with epilepsy. However, only limited empirical information exists to determine contemporary teachers' epilepsy knowledge and their confidence in instructing students with epilepsy

Methods: Following a structured scale-construction approach, a measure of teachers' knowledge and confidence was developed. The Teachers Epilepsy Knowledge and Confidence Scale comprises 14 Likert-type items of confidence and 25 multiple-choice fact (Knowledge) items. Two groups of teachers participated. Teachers-in-General (TiGs) were recruited on an entire school basis. At these sites, some teachers indicated they were currently teaching a student with epilepsy, forming a second group (Current Teachers, CT). Additional CTs were recruited on a teacher-by-teacher basis from the epilepsy practice at Phoenix Children's Hospital. The project was reviewed by university-based and hospital-based IRBs; it was funded by the Epilepsy Foundation (Patricia L. Nangle Fund). These are preliminary data from that study

Results: CTs ($n = 91$) expressed greater confidence than those not currently teaching a student with epilepsy (TiGs, $n = 203$) in their ability to meet an array of instructional, safety and psychosocial requirements. This was true even when between-group differences in teachers' prior background in special education, which was itself related to confidence, was controlled for statistically, $F(1, 293) = 34.97$, $p < .001$, $ç2 = .11$. However, neither group expressed a high absolute level of confidence: for CTs, average confidence ratings fell between "somewhat confident" and "between confident and unsure" (mean = 3.6 on a 5-point Likert scale), and for TiGs between "between confident and unsure" and "somewhat unsure" (mean = 2.8). Concerning knowledge, CTs responded correctly to more multiple-choice items assessing school-relevant epilepsy facts than TiGs, even after controlling for special education background, $F(1, 293) = 5.75$, $p = .017$, $ç2 = .02$. Both groups of teachers, however, knew less than one-half of the facts (CTs mean = 10.6; TiGs mean = 8.7 of 25 items). Among the sample as a whole, there were misconceptions about epilepsy (e.g., "partial" seizures denote students with partial impairment; epilepsy is synonymous with eligibility for supports based on Section 504 of ADA; epilepsy is not associated with risk for attention problems nor risk of depression; computers are not a seizure trigger for photosensitive patients). As expected, more knowledgeable teachers expressed greater confidence, $r = .43$, $p < .001$

Conclusions: Findings suggest that: (1) teachers, whether currently instructing a student with epilepsy or not, lack some important knowledge, (2) greater confidence and knowledge characterize teachers currently instructing a student with epilepsy and those with special education backgrounds, and (3) more knowledgeable teachers are generally more confident. It appears that additional information needs to be provided teachers. Results from this survey help suggest facts requiring supplemental dissemination to educators

2.022

EXPERIENCE IN ELECTROENCEPHALOGRAPHY DURING NEUROLOGY RESIDENCY

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Rationale: Exposure to EEG is one of the essential learning components of neurology residency program. However, there is no specific minimal requirement of EEG exposure assigned by ACGME or the American Board of Psychiatry and Neurology for neurology residency training. Typically, neurology residents spend 1 to 3 months in learning EEG during their training. Despite the fact that many hospital credential processes require specific number of EEG reading experiences, it is not clear how much of experience is sufficient for such credentialing. We conducted the study to evaluate the EEG experience for neurology residents during their training.

Methods: We reviewed all electroencephalogram reports that were performed at the Barrow Neurological Institute from January 1 to December 31, 2009. The reports were then identified whether they were dictated by rotating residents under attending physicians' supervision. These reports were reviewed to collect patient demographics, indications for obtaining EEG, and findings of specific abnormalities.

Results: 6403 electroencephalograms were performed at the Barrow Neurological Institute from January 1 to December 31, 2009. 378 EEG's were read and dictated by neurology residents under qualified electroencephalographers (average of 29.08 EEGs per resident per each rotation of 4-week block). There were 175 male and 203 female patients, and consisted of 3 neonatal EEGs (age 0-1 month), 9 infants (age 1-12 months), 24 toddlers (aged 1-3 years), 65 pediatrics (age 3-9 years), 68 adolescents (age 9-16 years), 162 adults (age 16-65), and 47 geriatric EEGs (age >65 years). Most EEGs were performed to evaluate possible seizure disorders (260), followed by transient neurological deficits (34), encephalopathy (29), syncope (20), memory problems (14), headache (5), developmental disorders (5), behavioral disorders (3), and brain death (2). Out of 378 EEGs, 207 were normal and remaining 171 were abnormal. The abnormalities of EEG included diffuse background slowing (96), focal epileptiform discharges (61), focal slowing (58), generalized epileptiform discharges (22), discrete ictal patterns (17), multifocal epileptiform discharges (11), breach rhythm (9), intermittent rhythmic delta activities (7), periodic lateralized epileptiform discharges (5).

Conclusions: Since many hospital credentialing requires approximately 100 EEG reading experiences, neurology resident may have to spend 3 to 4 months on EEG rotation in order to be eligible for credentialing without fellowship training. However, our data indicates that neurology residents are exposed to a wide range of EEG abnormalities and normal EEG patterns.

2.023

IBE PROMISING STRATEGIES PROGRAM 2008: "EPILEPSY AT SCHOOL: TEACHING THE TEACHERS". EDUCATIONAL PLAN OF "ASSOCIAçãO BRASILEIRA DE EPILEPSIA" WITH TEACHERS OF ELEMENTARY SCHOOL

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Rationale: To evaluate trough questionnaires the knowledge about epilepsy of Elementary School teachers obtained in the Promising Strategies Program "Epilepsy at school. Teaching the teachers." of "Associação Brasileira de Epilepsia" (ABE), which is the official Brazilian branch of International Bureau for Epilepsy.

Methods: ABE developed a questionnaire composed by 35 multiple-choice questions concerning: concepts, definition and causes of epilepsy (10); treatment and adverse effects of antiepileptic medication (10); popular stigma about epilepsy (5); activities of people with epilepsy (PWE) (5); and finally, first-aid during epileptic seizures (5). Questionnaire was presented in phase (ph) 1 to teachers before the lecture "Epilepsy: Causes, Symptoms and Treatment" given by a health professional from ABE trough classical live class (CC) or by video-conference (VC) on "Rede do Saber's site" (http://www.rededosaber.sp.gov.br/portais/NotíciasConteúdo/tabid/369/language/pt-BR/IDNoticia/851/Default.aspx) and in ph 2 afterwards. Results were compared to a control group of 65 teachers that did not attend any lecture.

Results: Classical class was given in 4 cities of Brazil and VC was performed in state of Sao Paulo and it was transmitted to 74 cities, including Sao Paulo city, this latter with 12 sites. 1153 teachers were instructed either by CC 25% (288) or VC 75% (865). Most (78.5%) were female, aged between 18-68 years (mean 41.4) and had 12-18 years of education; 76.6% attended University and 21.1%, graduate studies; 50% affirmed to know PWE. Mean of right answers in ph 1 in CC was 78.4% (±10.1) and VC, 79.8% (±8.6) and in ph 2 in CC, 86.5% (±6.4) and VC, 86.8% (±7.1), reflecting increased knowledge in ph 2 ($p<0.001$) in both strategies (controls: ph 1, 78.2%±7.4; ph 2, 79.6%±8.6; $p>0.05$). Comparison of variability of combined action (CC+VC) between ph 1 (79.5%±8.6) and 2 (86.8%±6.8) was 9.9%±13.9 ($p<0.001$) (control group 2.3%±10.2; $p<0.001$, compared to CC+VC). The topics "popular stigma" and "first aid during seizures" had the lowest correct scores in ph 1 (CC+VC), 74.6% and 72.8%, respectively (controls 78.8±10.2 and 67.9±17.5). The highest gain (35.6%) in ph 2 was observed in "first aid" (controls 0.8±27.2, $p<0.001$) and the lowest (0.1%), in "popular stigma" (controls 1.7±26.4, $p>0.05$). There was a significant variation in the topic "first aid" in CC, 41.1% compared to VC, 33.3% ($p=0.009$).

Conclusions: The educational plan of "Associação Brasileira de Epilepsia" revealed good performance of teachers of Elementary School without significant differences between presentation modalities (CC/VC), although CC was more efficient to teach first aid during epileptic seizures. Popular stigma about epilepsy knowledge has not improved after the lectures and this subject still needs further research and efforts for better understanding and action planning.

Support: International Bureau for Epilepsy, Companhia de Seguros Aliança do Brasil, Secretaria de Educação do Estado de São Paulo.

2.024

ESTABLISHING A COMPREHENSIVE EPILEPSY SURGERY CENTER IN SOUTH AMERICA, THE DARTMOUTH - URUGUAYAN EXPERIENCE

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Rationale: According to the National Association of Epilepsy Centers (NAEC) there are more than 50 specialized epilepsy programs in the United States treating the 2.7 million Americans who suffer from some form of epilepsy, of which 25 - 30 % are intractable. Epilepsy News reports that nearly 50 million people worldwide suffer from some form of epilepsy, and of those, 85% live in developing countries where it is estimated that 70 - 90% do not receive treatment.

Methods: To support comprehensive epilepsy care in South America, a relationship between the Hospital de Clinicas in Montevideo, Uruguay and the Dartmouth-Hitchcock Medical Center in Lebanon, NH, based on professional exchange and friendship, was established.

Results: Phase I of this project included selection of an existing publicly funded epilepsy program, and verification of access to neuroimaging and neuropsychology. A dedicated and competent local epilepsy team was crucial. Donations of modern epilepsy monitoring equipment were obtained. Nine candidates for monitoring were determined at this time.

Phase II consisted of installing monitoring equipment and conducting scalp video - EEG monitoring in Uruguay. Seizures were recorded in six patients and a protocol for long - term monitoring was established.

Phase III involved the collaboration of Uruguayan and Dartmouth - Hitchcock neurosurgeons who jointly performed five temporal lobectomies in Uruguay with excellent outcomes. Further neurosurgical training was provided at the Dartmouth - Hitchcock Medical Center.

Phase IV completed this project when invasive EEG monitoring was established at the Hospital de Clinicas in 2010. One patient was monitored intracranially and went to surgery. Additional training in intracranial mapping and surgical techniques was provided at this time.

Throughout this project each team benefitted from the abilities and experiences of the other.

Conclusions: Comprehensive epilepsy surgery programs can be successfully established in emerging economies with determination and resourcefulness. Access to epilepsy surgery will benefit patients who otherwise would continue to suffer from the socio-economic impact of epilepsy.

This encounter was sponsored by private contributions and the Dartmouth-Hitchcock Medical Center. Additional funding and equipment was provided by the Ad-Tech Medical Instrument Corporation and Grass Technologies.

This project was initiated by Peter D. Williamson, MD.

2.025

USING AN ONLINE EPILEPSY DIARY TO ENHANCE SELF-MANAGEMENT BEHAVIORS OF PEOPLE WITH EPILEPSY

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Rationale: Understanding what people do to manage epilepsy is critical to improving epilepsy care. Tracking and recording seizures, managing treatments and side effects, communicating with the health care team, and providing seizure first aid are common strategies taught by health care professionals. While survey data offers insights into patient experiences or feelings, they do not observe and describe actual behaviors. An online epilepsy diary offers a unique way of assessing patient self-report of symptoms as well as behaviors used to track and treat their symptoms.

Methods: This study examined the experiences and self-management behaviors of people with seizures using an online epilepsy diary. The My Epilepsy Diary, found on the epilepsy.com website, allows users to record their medical history and ongoing seizures, symptoms and treatments. Users may create reports and action plans, view data in narrative or graph form, and set reminders to enhance compliance. Since its' inception, 5,885 user accounts have been created. A cross-sectional and retrospective approach was used with a convenience sample of all diary accounts (n=452) accessed between May 2 and June 2, 2010. De-identified data were analyzed retrospectively to examine the number of transactions for specific areas and the most frequently reported symptoms, medicines and behaviors. The use of antiepileptic drugs (AEDs) was determined by looking at the number and type of AEDs during one day of the study period. This method was employed to prevent inaccurate reporting of AEDs for patients who may have changed drugs during the study period. Most transactions were entered via the website (n=7,399), while the newer iphone/itouch method was used for 1,199 transactions.

Results: Seizures were recorded by 77.8% of users; 75.4% of 452 users recorded 11,568 individual seizures and 27.3% recorded 2,226 seizure clusters since they started their diaries. The most frequently used AEDs included levetiracetam, lamotrigine, carbamazepine, and sodium valproate. Only 22 to 31% of patients took these AEDs as monotherapy. The online epilepsy diary lets users track their medication usage; 44% used the diary to note that they took their AEDs, while 9.3% noted missed meds and 8.8% took extra AEDs at times. 121 tracked side effects in their diary; the most frequent ones occurred in 22% or more (of 121) and included behavior/mood changes, sleepiness, cognitive problems, dizziness, and headaches. One quarter of diary users (n=114) sent email(9.7%) or text messages(15.9%) as reminders to take AEDs doses. Further data analysis explores the stability of group data by evaluating trends of diary users at different time intervals and examines usage of other self-management tools in the My Epilepsy Diary.

Conclusions: The use of this online seizure diary captures experiences of people with epilepsy as they happen. What users do to manage their epilepsy, rather than what may be recommended, can be examined in a large sample of diary users. The diary can serve as a clinical tool to enhance self-management behaviors critical for effective epilepsy care.

2.026

MEDICAL IDENTIFICATION USE PATTERNS IN PATIENTS WITH EPILEPSY & METHODS TO INCREASE THEIR USE

Patricia E. McGoldrick and S. M. Wolf (Beth Israel Medical Center, New York, NY)

Rationale: Rationale: Persons with epilepsy are at risk for seizures, and injuries. Use of medical identification in this population is underutilized.

Methods: Methods: A survey of 100 patients (ages 6-50) with epilepsy (defined as two or more unprovoked seizures in the previous five years) was undertaken. Patients and parents were questioned about their use of medical identification (including medalert jewelry and wallet ID cards.) A formal questionnaire was used.

Results: Results: Less than 10% of this group of patients used medical identification at all. Even fewer consistently used it. Reasons varied from cost, to difficulty obtaining the ID, to privacy concerns.

Conclusions: Conclusions: Use of medical identification by persons with epilepsy is an important part of the treatment plan and may lead to better communication between ER staff and the primary neurology team. It presumably will also result in shorter ER stays, fewer hospitalizations and fewer mistaken arrests. Barriers to the use of medical identification were identified and ideas for increasing the use of medical IDs were implemented.

2.027

EARLY EDUCATION TEACHERS' KNOWLEDGE ABOUT EPILEPSY - HOW WELL ARE THEY PREPARED IN THEIR UNDERGRADUATE YEARS?

Janet Mifsud and J. Dempsey (University of Malta, Msida, Malta)

Rationale: Despite modern scientific advances in the diagnosis and therapy for epilepsy, individuals with epilepsy are often subject to discrimination, stigma or rejection in the society, especially during their early education years. Moreover, the unpredictability of seizures in terms of their nature, timing, severity, and the situations in which they occur also cause difficulties for people with epilepsy (PWE) from doing well in their early education. Nonetheless, as suggested by numerous studies, it is believed that measuring the knowledge and attitudes toward epilepsy in education is a necessary initial step in ameliorating the understanding of and eliminating discrimination surrounding this condition, thus improving the quality of life of these children.

Methods: The aim of the study was to explore the knowledge and attitudes toward epilepsy in undergraduate students reading for the degree of Bachelor of Education (B. Ed.) in Primary studies at the University of Malta. By using a descriptive design, a thirty eight-item self administered questionnaire was delivered to a convenience sample of 36 second and third year students.

Results: The results showed that even though all the respondents claimed to know about epilepsy, there was significant deficits in terms of familiarity and specific knowledge about Moreover, the majority of respondents (85%) considered epilepsy as a condition from which people rarely recover and which hinders employment eligibility. Responses to a series of attitude related questions and statements indicated that while most held favourable attitudes, some (14%) objected to a relative from marrying someone with epilepsy or would not disclose a relative's epilepsy. Three respondents were reluctant to teach a student with epilepsy in their future career as school teachers. Furthermore, a considerable proportion (55%) believed that persons with epilepsy are more likely to have belligerent and antisocial traits than others. These responses were predominantly influenced by participants' previous experience with epilepsy in terms of seizures ($p < 0.05\%$).

Conclusions: Nevertheless, the findings disclosed by this study compare favourably with those presented in similar surveys concerning students' perceptions about epilepsy, and provide a useful starting point for future population-based surveys and educational campaigns in small island states such as Malta.

2.028

RESIDENT PHYSICIAN ACTIVITY RECOMMENDATIONS FOR PATIENTS WITH SEIZURES

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Rationale: Patients with seizures may have a diminished quality of life from activity restrictions put in place by physicians concerned that seizure-related injury may occur. Some literature suggests that seizure-related injury is uncommon. Care should be taken to not recommend excessive restriction of activities. Our aim was to determine how resident physicians counsel patients with seizures on driving, dangerous work conditions, recreation, and activities of daily living (ADL).

Methods: Investigators recruited internal medicine, neurology, neurosurgery, and pediatrics resident physicians to complete a pilot survey. In the survey, patients experienced complex partial seizures and "controlled" seizures were defined as being seizure-free for 6 months. Survey participants received the Florida Department of Highway Safety and Motor Vehicles (F-DOHSM) guidelines for applicants with seizures after survey completion for driving recommendation education.

Results: A total of 28 residents completed the survey, including 4 internal medicine, 11 neurology, 4 neurosurgery, and 9 pediatric residents. Level of training ranged from post-graduate year one to five. Most residents n=22 (78.6%) reported driving precautions counseling. Twenty one (75.0%) residents knew that, in Florida, patients should be seizure-free for 6 months before requesting reinstatement of driving privileges from the F-DOHSM. Seventeen residents (60.7%) reported counseling on dangerous work conditions including standing at a height, operating heavy equipment or power tools, or lifting heavy objects. Nineteen (67.9%) residents felt patients should be compliant with anti-epileptic medication and have controlled seizures before working under these conditions. Seventeen (60.7%) felt safety equipment and supervision should be in place, and 9 (32.1%) thought the patients' employer should be aware of the seizure diagnosis. Most residents, n=22 (78.6%) reported counseling on sports and recreation. Twenty six (92.8%) residents felt patients with controlled seizures can swim with supervision. However, for patients with uncontrolled seizures, 19 (67.9%) residents recommended no swimming regardless of supervision. When asked about specific sports, residents allowed greater participation for those with controlled versus uncontrolled seizures (Table 1 and 2). Golf and tennis were most commonly allowed. Gymnastics, hockey, and speed skating were least commonly allowed.

Twenty two (78.6%) residents reported ADL counseling. Fifteen residents (53.6%) recommended no bathing restrictions for controlled seizure patients. Bathing with supervision was most commonly recommend n= 19 (67.9%) for uncontrolled seizure. Showering only was recommended by 8 (28.5%) for uncontrolled seizures, and 5 (17.9%) for controlled seizures.

Conclusions: Resident physicians play an important role in activity counseling for patients with seizures. Education on activity recommendations would likely be beneficial for resident physicians and patients with seizures, and further research to develop recommendation guidelines is needed.

IMAGE: images/905322_A.jpg

IMAGE: images/905322_B.jpg

2.029

PREDICTORS OF FALLS AMONG PATIENTS ADMITTED IN EPILEPSY MONITORING UNIT: A RETROSPECTIVE CASE-CONTROL STUDY

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Rationale: Fall is an important adverse event encountered in the Epilepsy Monitoring unit (EMU). Risk factors or predictors of fall have never been studied among patients admitted to an epilepsy monitoring unit. The development of successful EMU-based interventions to decrease fall rates and fall-related injury requires large, well-designed studies to characterize the nature of falls and identify predictors of fall related injury.

Methods: A retrospective case control study through evaluation of patient medical record and incident reporting following fall in patients admitted in the Barrow Neurological Institute Adult Epilepsy Monitoring Unit. Cases were defined as patients admitted in EMU and had a fall. Controls were patients who had a fall during inpatient stay in neurology ward but did not have seizures. Time period of study was from 2006 to 2009.

Results: A total of 54 patients had 61 falls during the study period. 18 patients (cases) with 18 falls in EMU were studied against 36 inpatients (controls) with 43 falls. The mean age for cases and controls were 48 years and 59 years respectively. Of the 18 patients who had fall during EMU admission: 11 (61%) had average 3-10 seizures per month, 14 (77%) were on 1-3 antiepileptic medications, and 13 (72%) had prior seizure related falls(in comparison to 0% patient with no prior fall in control group). Majority of the falls happened during the first 3 days of EMU admission (N=11; 61%) and in evening 3 PM-11 PM (N 15; 83%). Toilet or bathroom is the commonest place to have fall (N=13; 72%) and most of them happened during ambulation (N=11; 61%). 94 % (N=17) of patient did not have any serious injury. All the patients (N=18, 100%) were identified as "high risk for fall" prior to EMU admission by using standardized fall risk assessment protocol adopted by the hospital. However in spite of this falls were not prevented. When compared to controls, there was no significant difference in number of risk factors identified by the assessment protocol.

Conclusions: Risk factors of fall among patients admitted in EMU are not significantly different from as that of general inpatient admission. Despite the fact that high-risk patients were identified by using standardized fall risk assessment, falls were not prevented. Therefore, this study indicates that implementation of policy should be addressed more rigorously in high-risk patients for fall.

2.030

CORRELATION BETWEEN EEG FINDINGS AND LANGUAGE LATERALIZATION FOR INTRACAROTID AMOBARBITAL PROCEDURE IN CHILDREN

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Rationale: Background: Intracarotid amobarbital procedure (IAP) is considered the gold standard for language lateralization. EEG changes during IAP are well defined, but how these EEG changes correlate with IAP interpretation and neurobehavioral findings are not defined. This study correlated the EEG findings with the clinical and neuropsychological test results (language score and memory testing) in children who underwent IAP for refractory epilepsy.

Methods: Method: Fifty consecutive children who underwent IAP test at Texas Children's Hospital between 2004-2009 were retrospectively reviewed. Injection was first administered to the carotid artery ipsilateral to the pathological hemisphere. IAP was considered conclusive (CON) for language lateralization if aphasia or paraphasia occurred and inconclusive (INCON) if IAP was aborted due to agitation and/or obtundation. Digital trending analysis was used to quantify EEG findings in the 43 available EEGs.

Results: Results: Mean age was 13.5±2.8 (range: 8-18 years). Thirty-five were right ® handed and 10 left (L) handed. The seizure focus was on the left in 32 and on the right in 12. Average full scale IQ was 88 (range 52 to 119). Amobarbital dose ranged from 60 to 150 mg (mean: 107±19.9); additional amobarbital was required in 23. Angiography showed no contralateral cross-filling and no seizures occurred during the IAP.

EEG changes occurred within 10 seconds following injection, becoming maximum between 60-90 seconds. Ipsilateral EEG changes occurred in 34; early onset bilateral (BL) changes within 30 seconds in 10; a fast rhythm occurred in only 9. Although contralateral arm weakness occurred in all, sustained EEG changes did not occur in 11.

Clinically, 34 children developed aphasia with ipsilateral injection; bilateral language representation was suspected in 2; no aphasia occurred in 3; IAP was INCON in 7. The ICON group had a lower mean age versus the CON group (10.8±3.0 vs 14±2.5 years) (p: 0.006). Although the INCON group had a lower amobarbital dose, EEG showed higher amplitude, sustained ipsilateral slowing with L sided injection at 30 seconds (133±119 vs 119±51uV) (p: 0.014). BL EEG changes occurred more often in the INCON compared to the CON group (57% vs 17%, p: 0.043).

Conclusions: Conclusion: Ipsilateral EEG changes are associated with language lateralization with CON IAP results. Younger ages and bilateral EEG slowing are predictors for INCON IAP results. The IAP may be CON even when contralateral arm weakness occurs with only minimal EEG changes.

2.031

PERIODIC LATERALIZED EPILEPTIFORM DISCHARGES (PLEDS): CLINICAL SIGNIFICANCE, NEUROIMAGING FINDINGS, ETIOLOGY, AND OUTCOME IN 51 INFANTS AND CHILDREN

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Rationale: In adult series periodic lateralized epileptiform discharges (PLED) have usually been reported transiently during acute stroke, infection, or hypoxic encephalopathy. Data on PLEDs in children are limited to small case series. We report clinical and radiological features of 51 children (<18 years) with PLEDs on a scalp EEG.

Methods: The EEG database at the Cleveland Clinic from 1990-2000 was searched using the key word "PLED". Patients < 18 years were identified and their medical records and brain imaging were reviewed.

Results: 89 EEGs on 51 children (6 days to 18 years, median 6.5 years) showed unilateral or bilateral PLEDs. In 14 of 51 (27%), PLEDs occurred after an acute or subacute neurological illness in previously healthy children (acute group) with acute infections and stroke being the most common etiologies. In the remaining 37 children (73%), PLEDs were seen in the setting of a pre-existing neurological illness (chronic group). All children in the chronic group had developmental delay and neurological deficits. In the chronic group, 14 (37%) developed new PLEDs (acute on chronic group) during seizure recurrence with or without status epilepticus while 23 (62%) had no acute worsening in their neurological status and PLEDs were a chronic finding in the setting of a malformation of cortical development (9), prior epilepsy surgery (7, no PLEDs before surgery), encephalomalacia from remote trauma (2) or stroke (2), and metabolic encephalopathy (2). Children with remote epilepsy surgery (n=7) were seizure free despite post-operative PLEDs. All other children in the chronic group had epilepsy. Mortality was high with 9 deaths out of 28 (32%) in acute and acute on chronic group compared to 2 out of 23 (8.5%) with chronically present PLEDs. Of 23 with chronically present PLEDs, 22 children had an EEG and clinical follow-up for 5 months to 9 years (median 4.5 years). 2 with metabolic disease died (both had BiPLEDs), 4 underwent hemispherectomy (3) or fronto-parietal resection (1) with disappearance of PLEDs and seizures after surgery, 7 with remote epilepsy surgery were seizure free, and 9 with inoperable MCD, remote head trauma and infarcts continued to have PLEDs or BiPLEDs and chronic persistent seizures on follow-up EEGs.

Conclusions: While acute brain injury remains an important cause, PLEDs in children are more likely to be associated with preexisting chronic neurological condition with or without acute exacerbation. This recognition is important to avoid over emphasis on EEG, and relying on the clinical evaluation to guide further management in children.

2.032

INTERICTAL FAST OSCILLATIONS CAN BE RECORDED FROM SCALP EEG

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Rationale: Fast oscillations seem to play an important role in normal and pathological brain function. For useful clinical applications, it would be preferable to record fast oscillations non-invasively. This study aims to identify gamma and ripple bands on scalp EEGs of epileptic patients and analyses the association between them and interictal and ictal discharges.

Methods: Scalp EEG of 15 patients with focal epilepsy was low-pass filtered at 200Hz and sampled at 600Hz. Spikes and fast oscillations were visually marked during non-REM sleep samples of 30 min. High-pass filters at 40 and 80Hz were used to identify gamma (40-80Hz) and ripple band (80-200Hz) oscillations. Only events containing at least four consecutive oscillations and an amplitude clearly higher than the background were considered as fast oscillations. We analyzed the rates of gamma and ripples, their co-occurrence with spikes, the number of channels with fast oscillations inside and outside the seizure onset zone (SOZ), and the specificity, sensitivity and accuracy of gamma, ripples and spikes to determine the SOZ. SOZ was defined as the scalp area where the first ictal discharge prior or concomitant to the clinical onset was seen.

Results: We identified a SOZ in 8/15 patients. Gamma was recorded in all patients and ripples in 12. Averaging all 439 channels (approximately 31 channels per patient), the rates were: spikes (1.7 ± 1.13/min), gamma (0.35± 0.35/min) and ripples (0.16 ± 0.24/min). Gamma and ripples co-occurred with a spike in 77.5% and 63% (fig. 1 and 2), and spikes co-occurred with gamma in 14.5% and with ripples in 7%. In only two patients gamma and ripples were recorded on non-spiking channels. There was a positive correlation between rates of spiking and rates of gamma ($p<0.0001$) or ripples ($p<0.0001$). In the eight patients with a defined SOZ, 44 channels were inside the SOZ and 195 outside. For all events, the number of channels inside the SOZ was consistently higher than outside: spikes {44/44 (100%) vs. 137/195 (70%), $p<0.0001$}; gamma {36/44 (82%) vs. 63/195 (32%), $p<0.0001$}; and ripples {21/44 (48%) vs. 22/195 (11%), $p<0.0001$}. The number of channels in which spikes co-occurred with gamma {31/44 (70.5%) vs. 47/195 (24%), $p<0.0001$} or ripples {16/44 (36%) vs. 15/195 (8%), $p<0.0001$} was also significantly higher inside than outside the SOZ. For all events, the mean rates were higher inside than outside the SOZ: spikes (2.64 ± 1.70 vs. 0.69 ± 0.26, $p=0.02$); gamma (0.77 ± 0.12 vs. 0.10 ± 0.16, $p=0.02$); and ripples (0.08 ± 0.12 vs. 0.04 ± 0.09, $p=0.04$). The sensitivity, specificity and accuracy to identify the SOZ were 100%, 30% and 43% for spikes; 82%, 68% and 70% for gamma; and 48%, 89% and 81% for ripples.

Conclusions: Gamma and ripples can be recorded by scalp EEG and have a significant relationship with interictal spikes. The rates of fast oscillations and the number of channels with gamma or ripples are higher inside the SOZ, indicating that they may be used as interictal scalp EEG marker for the SOZ. These events are less sensitive but much more specific or accurate than spikes to delineate the SOZ.

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IMAGE: images/903727_A.jpg

Figure 1. Representative examples of interictal Gamma. (1) Gamma co-occurring with spike with oscillations visible during spike. (2) Gamma co-occurring with spike with oscillations not visible during spike, but visible after filtering. (3) Gamma independent of spike. (A) Raw EEG. (B) Raw EEG with expanded time. (C) EEG filtered with high-pass filter of 40 Hz. Note different amplitude calibrations.

IMAGE: images/903727_B.jpg

Figure 2. Representative examples of interictal Ripples. (1) Ripples co-occurring with spike with oscillations visible during spike. (2) Ripples

co-occurring with spike with oscillations not visible during spike, but visible after filtering. (3) Ripples independent of spike. (A) Raw EEG. (B) Raw EEG with expanded time. (C) EEG filtered with high-pass filter of 80 Hz. Note different amplitude calibrations.

2.033

HIGH FREQUENCY OSCILLATIONS (HFOS) IN PATIENTS WITH REFRACTORY EPILEPSY AND NORMAL MRIS

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Rationale: Patients with intractable focal epilepsy and normal MRIs have generally a less favourable surgical outcome compared with those with lesional epilepsy. This is usually explained by the lack of a reliable marker of the epileptic tissue. Since HFOs may have clinical value as biomarkers for epileptogenesis, we hypothesized that their presence would provide a more accurate localization of the epileptogenic tissue, favoring a better prognosis.

Methods: Intracerebral EEGs (iEEGs) were recorded in 17 patients with intractable focal seizures and normal MRIs. The iEEG was low-pass filtered at 500 Hz and sampled at 2000 Hz. Spikes and HFOs were visually marked in 5 or 10-min slow wave sleep samples. High-pass filters at 80 and 250 Hz were used to identify ripples and Fast Ripples (FRs). We analyzed the rates of HFOs and the number of channels with HFOs inside and outside the seizure onset zone (SOZ). We assessed the specificity, sensitivity and accuracy of ripples, FRs and spikes to determine the SOZ and their relation with post-operative outcome. We considered Engel class I and II as good outcome and Engel class III and IV as poor outcome.

Results: The SOZ was temporal (71%), occipital (18%) or frontal (6%) in the 16 patients where it was defined. Seizures originated from more than one distinctive area in seven patients (41%). Thirteen patients (76.5%) underwent surgery: 6 (46%) had a good and 7 a poor outcome. The mean rate of spiking was higher in the SOZ channels than in the non-SOZ channels (16.03 ± 10.50/min vs. 4.11 ± 3.33/min; p=0.0002); similarly for ripples (43.4 ± 32.7/min vs. 10.8 ± 11.6/min; p=0.0016) and FRs (10.2 ± 11.0/min vs. 2.0 ± 3.5/min, p=0.0047). The sensitivity, specificity and accuracy to identify the SOZ were for spikes 91%, 29% and 44%; for ripples 91%, 42% and 54%; and for FRs 64%, 80% and 76%. We found no correlation between the number of channels and rates of ripples and FRs inside and outside the SOZ and postoperative outcome. In the seven patients with more than one SOZ, 5 with bitemporal lobe epilepsy showed a clear preponderance of one generator. They underwent a resection on the side of the main SOZ. We analyzed the relationship between the relative rates of ripples and FRs in the secondary SOZ and post-operative outcome. When relative rates of HFOs in the non-resected SOZ were high, the post-operative outcome was poor.

Conclusions: Analysis of interictal HFOs during 5-10 min of sleep recording is a good tool to localize the SOZ in patients with epilepsy and normal MRI, given that the rates of HFOs were significantly higher in SOZ than in non-SOZ channels. We did not find any correlation between the post-operative outcome and the rates of HFOs. Interestingly, in patients with more than one identified SOZ when the relative values of HFOs were high in the non-resected SOZ, the post-operative outcome was poor. This suggests a participation of these secondary SOZs to the continuation of seizures after surgery.

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2.034

PSEUDO-TEMPORAL ICTAL PATTERNS COMPARED TO TRUE TEMPORAL ICTAL PATTERNS

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Rationale: A pseudo-temporal ictal pattern refers to an EEG ictal pattern that is mis-localized to the temporal region when the epileptogenic zone is actually outside of the temporal lobe. They are misleading and can lead to faulty pre-surgical localization. Our aim is to analyze the EEG features of patients with pseudo temporal ictal patterns and differentiate them from patients with “true” temporal lobe epilepsy if at all possible.

Methods: We retrospectively identified 10 patients (37 szs) with pseudo-temporal (PT) ictal patterns chosen based on their presurgical EEG reports of temporal ictal patterns, and preliminary visual confirmation by one of us (SE). They included 5 frontal, 3 parietal, 1 insular and 1 occipital lobe epilepsy patients who had extratemporal surgery. They were compared with 12 patients (45 szs) with mesial temporal epilepsy due to pathologically proven hippocampal sclerosis (HS), and 11 (41 szs) with neocortical temporal epilepsy (NT) who had lateral temporal resections with preservation of mesial structures. All patients had an Engel class I outcome for a minimum of one year after surgery. Interictal discharge populations were compared amongst the 3 groups. Structured visual analysis of up to 5 seizures in each patient was performed by two blinded investigators (NS, RE) using the full capabilities of digital EEG in bipolar and referential montages for ictal onset and later significant ictal patterns with regards to frequency, location, timing, duration, and spread. Source analysis using FOCUS in BESA 5.1 was performed by one blinded investigator (RE) on the first 5-10 seconds of EEG ictal onset from the best artifact free seizure of each patient and classified as temporal or extratemporal.

Results: The distribution of scalp interictal discharges overlapped amongst the 3 groups. The distribution of ictal patterns in PT group in terms of location and duration were not separable from those in “true” temporal groups. In PT group 9/37 Szs (6 pts) started with regional temporal patterns (4 rhythmic delta, 4 rhythmic theta, 1 rhythmic alpha), and rhythmic temporal theta was seen in 8 szs of 5 pts as a later significant pattern. All seizures in PT group spread to the contralateral side while 13 szs (6HS, 7 NT) of 4 pts in “true temporal” groups did not show contralateral spread ($P < 0.05$). Source analysis did not improve the separation amongst groups.

Conclusions: Pseudo-temporal ictal patterns are morphologically indistinguishable from “true” temporal ictal patterns by visual or source analysis. Rhythmic temporal theta at ictal onset or as later significant pattern can be a spread pattern in extra-temporal epilepsy. One possible differentiating point is that while all PT seizures showed bilateral spread, temporal ictal patterns that remained strictly unilateral without contralateral spread were only found in “true” temporal lobe epilepsy. The findings support the notion that once activated, whether from an intrinsic generator or by extrinsic propagation, the temporal lobe structures can generate a more or less identical electrical seizure discharge.

2.035

OCCURRENCE OF HIGH FREQUENCY OSCILLATIONS DEPENDS ON PATHOLOGY IN PATIENTS WITH FOCAL CORTICAL DYSPLASIA

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Rationale: Patients with focal cortical dysplasia (FCD) often suffer from intractable epilepsy. FCDs are grouped depending on pathology according to Palmini type 1a, 1b, 2a and 2b. There is conflicting evidence on whether the type of pathology is relevant for the prognosis of epilepsy. High frequency oscillations (HFOs, 80-500Hz) are linked to epileptic areas and their occurrence is more closely linked to the seizure onset zone than to lesional areas. Small studies on patients with FCD showed differing results for the occurrence of HFOs, with some patients having very high and others rather low rates of HFOs within the lesion. This study investigates the correlation between different types of FCDs and the generation of HFOs.

Methods: Consecutive patients with FCD that were recorded with intracranial grid electrodes at the Freiburg Epilepsy centre with a 450Hz low pass filter and a sampling rate of 1024Hz were included. Postsurgical pathology was classified after Palmini. Ripples (80-200Hz) and fast ripples (200-450Hz) were visually identified by two independent reviewers during 5 minutes of slow wave sleep. Rates of HFOs were calculated for each channel and compared in areas inside and outside the seizure onset zone (SOZ) and patients with FCD type 1a&b with type 2a&b using ANOVA ($p<0.05$).

Results: Twenty-one patients were included, with four having FCD type 1a, five type 1b, nine type 2a and five type 2b. HFO rates were significantly higher inside than outside the SOZ for all lesion types ($p<0.001$) and less common in patients with FCD types 1a&b than in FCD types 2a&b (ripple $p<0.001$, fast ripple $p= 0.02$) (Figure 1). Other clinical features (# of channels implanted, seizure frequency, postsurgical outcome) did not differ with the pathology. HFOs were not limited to the SOZ areas but also visible in areas adjacent to the SOZ within the FCD (Figure 2). Two types of HFO patterns were observed: pattern 1 was defined as channels with a continuously oscillating baseline with intermittently occurring higher voltage HFOs, with pattern 2 channels had a flat baseline without HF activity and intermittent very high voltage HFOs. The probability of pattern 2 being associated with the SOZ was significantly higher than in pattern 1 ($p<0.05$).

Conclusions: HFOs are significantly correlated with the SOZ in patients with different types of FCD. Other areas of the lesion may also generate lower rates of HFOs. HFO patterns of occurrence may be important for the interpretation of their meaning; those occurring in channels with non-oscillating baselines were more closely linked to the SOZ than those occurring in continuously oscillating baselines.

In FCD of Palmini type 1a&b, HFOs were rare compared to FCD type 2a&b, even if other clinical features did not vary between the different pathologies. Our study may indicate that generation of HFOs is more facilitated in patients with FCD type 2a&b and this may be related to the specific pathology. The generation mechanisms of pathological HFOs still remains unclear and thus reasons for the difference in HFO generation remain speculative.

IMAGE: images/905705_A.jpg

IMAGE: images/905705_B.jpg

2.036

UTILITY OF STAT EEG IN A TERTIARY CARE INSTITUTION

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Rationale: Emergent/stat electroencephalogram (sEEG) is a tool utilized to identify patients in non-convulsive status epilepticus (NCSE), especially in patients with unexplained mental status change. Previous smaller studies have evaluated the indications and usefulness of sEEG [1-2], with some arguing that neurological consultation is needed prior to obtaining a sEEG [3]. The primary objective of our study was to evaluate the utility of sEEG in detecting discrete seizures or status epilepticus as a function of ordering physician and clinical indication.

Methods: We performed a retrospective review of all sEEGs reports at the Barrow Neurological Institute for the year 2008. sEEG is available 24 hours a day and are performed at the request of any ordering physician, except between 6 PM to 6 AM, and on weekends, when they must first be approved by a clinical neurophysiologist. All reports were reviewed for the parameters listed in Table 1. Statistical analysis was performed using either chi-squared or Fisher's exact test.

Results: Of the 3,471 inpatient EEGs performed in our institution during the review period, 778 (22.4%) were sEEGs. Patients ranged in age from 4 days to 95 years (median age of 54 years). 49% of the patients were male. 3.5% (n=27) of all sEEGs demonstrated NCSE, while 0.4% (n=3) and 1.2% (n=9) revealed convulsive status epilepticus or discrete electrographic seizures, respectively (table 1). Although our volume has since increased by 7-fold, this yield did not differ significantly from 2005 data obtained at our institution [4]. Neurologist had the highest rate of finding status epilepticus (SE) or seizures at 7.3%, followed by intensivists (7%), neurosurgeons (4.1%), and other services (3.3%). However, there was no statistically significant difference among ordering physicians ($p=0.20$). The most useful clinical indicators for predicting SE or seizure were overt, continuous seizures and witnessed seizure without return to baseline ($p<0.001$)(table 2).

Conclusions: In our tertiary care institution sample, the rate of finding SE or seizures among sEEG is 5.1%. In our sample, the best clinical predictors of finding NCSE or discrete seizures on a sEEG are overt, continuous seizures or witnessed seizure without return to baseline. Additional monitoring methods, such as continuous EEG, should be considered in critically ill patients for improved yield. Furthermore, our data suggests that perhaps neurological consultation should NOT be mandatory prior to obtaining a sEEG.

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IMAGE: tables/904868_T1.jpg

Figure 1. sEEG parameters and results. CNS-central nervous system; ALOC- altered level of consciousness; ICU-intensive care unit; ED-emergency department; NCSE-non-convulsive status epilepticus; CSE-status epilepticus.

[a]One EEG result categorized as 'Other' due to lack of cerebral activity.

IMAGE: tables/904868_T2.jpg

Figure 2. Percentage yield of sEEGs based on clinical indication. Yield was calculated as a percentage of the sEEGs revealing status epilepticus or seizure pattern to the total number of sEEGs ordered for a particular clinical indication.

*$p<0.001$, with standard residual value >2, indicating significance.

2.037

ENHANCED INTRACORTICAL INHIBITION: A CORTICO-CORTICAL EVOKED POTENTIAL STUDY

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Rationale: Epileptic conditions are characterized by an altered balance between excitatory and inhibitory influences at the cortical level. Interictal "homeostasis" is maintained in part by intracortical inhibitory mechanisms. Intracortical excitation and inhibition can be investigated in vivo with cortico-cortical evoked potentials (CCEP). We hypothesized that during the interictal state, CCEPs obtained from stimulation of the ictal onset zone will have a relatively restricted distribution as compared to stimulation of cortices remote from this region. This may be due to a region of enhanced intracortical inhibition surrounding the ictal onset zone.

Methods: We retrospectively reviewed CCEPs obtained in patients who underwent intracranial EEG evaluation with subdural grid electrodes (with or without additional depth electrodes) between 2008 and 2010. We identified patients with CCEPs recorded with similar stimulation parameters from both the ictal onset zone in addition to a region remote from the ictal onset zone (preferably a separate lobe). We then compared the distribution of CCEPs obtained from the highest stimulus intensity.

For CCEP acquisition, we used bipolar electrical stimulation of adjacent paired subdural electrodes with a constant-current square wave pulse of 0.3 ms duration at a fixed frequency of 1 Hz. The polarity of the stimulus current was alternated. The stimulus intensity ranged from 1-15 mA. The electrocorticogram was then averaged 60 times with a time window of 200 ms time-locked to the stimulus.

Results: We identified five patients who met our inclusion criteria. We studied the distribution of CCEPs obtained from five ictal onset zones in comparison to six remote regions of cortex. In four out of five of our patients, the distribution of CCEPs obtained from stimulation of the ictal onset zone was relatively restricted in comparison to that obtained from stimulation of remote cortices.

Conclusions: Cortico-cortical evoked potentials provide a method of studying intracortical inhibition and excitation in epileptic patients. There appears to be a significant difference in the distribution of CCEPs recorded from the ictal onset zone as compared to cortical areas remote from this region. The restricted distribution of CCEPS recorded from the ictal onset zone during the interictal state may in part be a result of enhanced intracortical inhibitory mechanisms. Recognition of these CCEP patterns may help in identifying epileptogenic cortical regions.

2.038

EXTENT OF THE INTRACRANIAL ICTAL ONSET ZONE IN SEIZURES WITH AND WITHOUT ICTAL SCALP EEG PATTERN: A CASE-CONTROL STUDY

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Rationale: Simple partial seizures frequently escape scalp-EEG detection. Ictal EEG patterns in such seizures can be better detected on intracranial EEG (ICEEG). The location, orientation, extent, and degree of synchrony of the generating source, are factors determining the appearance of epileptic activities on scalp. We aimed to compare the extent of the intracranial ictal onset zone in patients with scalp-EEG undetectable seizures to patients with scalp-EEG positive seizures arising from identical sublobar regions. No previous systematic studies addressing this question in patients with epilepsy arising outside the temporal lobe were found in the published literature.

Methods: We retrospectively reviewed the records of 426 patients who underwent ICEEG for epilepsy surgery from 1997-2008. Of these, 69 patients had seizures or auras with no ictal EEG pattern on their preoperative scalp video-EEG recordings. Patients who had seizures with identical semiology both during their scalp-EEG and subsequent ICEEG evaluation were included. Cases were age-matched to control patients, who had scalp-EEG positive seizures preoperatively, arising from an identical sublobar region on ICEEG, according to the Talairach system. The extent of the intracranial ictal onset zone was estimated by the number of ICEEG electrodes involved at ictal onset.

Results: A total of 18 cases were identified. There were no differences in demographic data, epilepsy classification, MRI findings, pathology results, or surgical outcomes between cases and controls. Average number of implanted contacts was 104 (36-184) in cases and 115 (48-184) in controls ($p=0.368$). A total of 289 seizures were analyzed (156 in cases and 133 in controls). Scalp undetectable seizures were associated with auras in 13 patients and simple motor seizures with or without aura in 5 patients. Intracranial ictal EEG onset was located on the lateral convexity in 9 patients, mesial aspect in 6 patients, and basal surface in 3 patients. Mean number of contacts involved at the ictal onset was smaller in cases (2.88+/-1.83) compared to controls (4.50+/-2.66) ($p<0.001$). This difference was also notable when examining each of the 3 surfaces of the brain separately: lateral convexity (2.89+/-1.99 vs 4.58+/-3.54) ($p=0.020$), mesial aspect (3.46+/-1.73 vs 4.44+/-2.12) ($p=0.031$) and basal surface (2.32+/-1.14 vs 4.53+/-0.96) ($p<0.001$). On the whole, the estimated size of the ictal onset region was 2-3cm2 in cases and 4-5cm2 in controls.

Conclusions: Our data examining a large area of cortical regions indicate that the extent of the ictal onset zone, as defined by ICEEG, is significantly smaller in patients who have simple partial seizures that are invisible with scalp-EEG recordings, compared to patients whose

identical seizures are detectable on scalp-EEG. In this study, 50% of patients with scalp-EEG undetectable seizures were found to have seizures arising from the lateral convexity. Hence, even seizures that arise from more superficial sources can be frequently undetectable by scalp-EEG.

2.039

THE ADDED VALUE OF INTRACEREBRAL SEEG RECORDINGS IN THE PRE-SURGICAL EVALUATION OF REFRACTORY FOCAL EPILEPSY CASES

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Rationale: Intracerebral depth electrode EEG (SEEG) studies are considered in patients with medically refractory focal epilepsy after non-invasive investigation failed to provide a satisfactory answer on the brain region(s) responsible for the generation of their seizures. SEEG is a technique used in our institution since 1972 with a low morbidity (De Almeida et al. J Neurosurg 2006;104:480). The number of electrodes to be inserted in each case is however limited by the invasiveness of the technique, and, hence, the value of the method to define the epileptic generator depends on an adequate a priori clinical hypothesis. The aim of the study was to determine the added value of SEEG to the pre-implantation clinical diagnosis in a heterogeneous group of patients with refractory temporal (TLE) or extra-temporal epilepsy (extra-TLE).

Methods: We retrospectively evaluated the clinical and SEEG data of 108 patients with refractory focal epilepsy consecutively investigated with SEEG between 2000 and 2007. In a first step, one of the investigator blinded to the SEEG evaluations reviewed for all patients the pre-implantation clinical, scalp EEG, imaging and neuropsychological data and classified them in one of the three following groups: 1) TLE; 2) extra-TLE; or 3) could not distinguish between TLE and extra-TLE. In a second step, the SEEG evaluations were reviewed to determine whether a single seizure generator, or multiple, widespread or no generator were found. Thirdly, we compared the clinical hypotheses with the SEEG findings and a decision was then made on whether SEEG: 1) confirmed the clinical hypothesis; 2) added more information; or 3) failed to identify a seizure generator. Finally, we reviewed the post-implantation decisions and, when applicable, surgical outcomes and correlated them with the clinical diagnosis and SEEG findings

Results: 108 patients were studied with intracerebral electrodes exploring the TL (n=33), extra-TL (n=14) or both structures (n=61). 67 patients (62%) had a lesion on MR imaging and 8 had a surgery prior to SEEG exploration. 38 patients were classified as TLE cases, 20 as extra-TLE, and in 50 we could not distinguish between TLE and extra-TLE. SEEG identified a single seizure generator in 56 (52%) patients, generators were multiple in 19 (17.5%) or widespread in 24 (22%), or SEEG failed to identify a generator in 9 (8%). In 19 patients (18%) a decision was made not to operate. In this group, SEEG identified a single focus in only 32%. 89 patients were operated (77 with a f/up >2 yrs). Those (30 pts) with a favorable surgical outcome (Engel's classes 1 and 2) were more likely to be found in the TLE group (15/30) or when a single focal generator could be defined by SEEG (18/30).

Conclusions: SEEG provided useful information in the majority of our patients with focal refractory epilepsy in which non-invasive investigation failed to identify a clear seizure generator. Overall, SEEG confirmed the pre-implantation hypothesis in 32% and added new information in close to 60% of them.

Table 1a. Proportion (%) of patients (n=108) in SEEG categories for each clinical classes

IMAGE: tables/893414_T1.jpg

Table 1b. Proportion (%) of patients (n=30) with a favorable (classes 1 and 2) surgical outcome.

IMAGE: tables/893414_T2.jpg

2.040

GENERALIZED PAROXYSMAL FAST ACTIVITY AND TONIC SEIZURES IN OLDER ADULTS

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Rationale: Generalized paroxysmal fast activity on EEG is typically associated with tonic seizures in the setting of Lennox-Gastaut Syndrome. However, adults can present with this pattern and have a different clinical course and response to therapy.

Methods: Four adults with abnormal movements had EEGs, clinical evaluations, and were treated with AEDs.

Results: Case 1. A seventy-six year old man with hypertension, diabetes, and a history of generalized tonic-clonic seizures developed jerking in the setting of non-adherence to anticonvulsant therapy. EEG showed bursts of generalized paroxysmal fast activity lasting 1 to 3 seconds, associated with tonic posturing of the trunk and head without alteration of consciousness. MRI showed periventricular white matter changes. Levetiracetam controlled the tonic seizures.

Case 2. A sixty year old man with hypertension, diabetes, and supraventricular tachycardia with implantable defibrillator presented with bizarre behavior, hallucinations, and jerking movements of the arms. He had no prior history of seizures. EEG showed bursts of generalized paroxysmal fast activity lasting 1 to 3 seconds, associated with tonic extension of the upper extremities and speech arrest (Fig 1). Head CT was unremarkable. Valproic acid significantly decreased the frequency of tonic seizures.

Case 3. A sixty-four year old woman with liver cirrhosis, mechanical mitral valve, coronary artery bypass graft, anemia, hyponatremia, and diabetic neuropathy on gabapentin, presented with a three year history of whole body jerking and stiffening. She had no prior history of seizures. EEG showed bursts of generalized paroxysmal fast activity lasting 1 to 3 seconds, associated stiffening of head and arms, followed by shivering of the arms, without an alteration of consciousness. MRI showed periventricular white matter changes. Levetiracetam controlled the tonic seizures, but she developed behavioral changes and was transitioned to lacosamide which also controlled the tonic seizures.

Case 4. A fifty-six year old man with diabetes and chronic kidney disease who had been treated for osteomyelitis developed jerking movements of his trunk and shoulders. He had no prior history of seizures. EEG showed bursts of generalized paroxysmal fact activity lasting 0.5 to 3 seconds, associated with tonic stiffening of trunk and facial muscles without an alteration of consciousness. MRI showed

periventricular white matter changes. Clonazepam controlled the tonic seizures.

Conclusions: We describe four cases of adults who presented with abnormal movements and were found to have tonic seizures that responded to AED therapy. Only one of the patients had a history of epilepsy, and all had complex medical histories and polypharmacy. Recognition of tonic seizures and differentiation from non-epileptic movements can play an important role in reducing morbidity in these patients.

IMAGE: images/905864_A.jpg

Case 2. Generalized paroxysmal fast activity.

2.041

DIAGNOSTIC YIELD OF EMERGENT EEG

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Rationale: Emergent EEG is frequently ordered by emergency physicians. This study was performed to assess the yield of emergent EEG in case of correct indication. To determine the correct indications, we used criteria adapted from the Tour guidelines (Neurophysiol Clin 1997; 27: 373-405 and Neurophysiol Clin 1998; 28: 103-153): an emergent EEG is required in case of acute confusion or coma to rule out non convulsive status epilepticus (NCSE), or in case of a possible first seizure to increase the chance of picking up interictal epileptiform discharges.

Methods: All EEGs with a correct indication requested by emergency physicians between 11-2009 and 05-2010 were prospectively included. Patient history, EEG findings and final diagnosis were reviewed. An EEG was considered useful if it showed epileptiform discharges in a patient with a final diagnosis of seizure/epilepsy or if it allowed confirming or excluding NCSE.

Results: Ninety-three EEGs were reviewed. The referring diagnosis were possible first seizure (69/93), acute confusional state (17/93) or coma (7/93). In the possible first seizure group, there were 51/69 episodes of transient loss of consciousness and 18/69 episodes of transient neurological symptoms.

Interictal epileptiform discharges were seen in 10/69 patients of the first seizure group, in 1/7 patient of the coma group and in no patient of the acute confusion group. Nine out of 93 EEGs showed focal discharges and 3/93 generalized discharges, including 2/93 with GPEDs (one patient had both focal discharges and GPEDs). Ictal activity, suggesting NCSE, was identified in 4 patients, all in the coma group.

The most common final diagnoses in the possible first seizure group were first seizure (25/69), syncope (14/69), non-epileptic psychogenic seizure (6/69), stroke or TIA (5/69) and migraine (2/69). No diagnosis was found in 10/69 patients.

In the acute confusion and coma group, the most common diagnoses were toxic/metabolic encephalopathy (6/24), dementia (6/24) and NCSE (4/24).

Patients with a final diagnosis of first seizure or de novo status epilepticus were diagnosed with either symptomatic epilepsy (13/26), cryptogenic epilepsy (3/26), primary generalized epilepsy (2/26), provoked seizures (6/26) or seizure of unknown origin (2/26). Among them, 9/26 patients had interictal epileptiform discharges and 1/26 was in NCSE. No epileptiform discharge was seen in patients with a diagnosis of syncope.

Of all the EEGs reviewed, 34/93 contributed significantly to the diagnosis by showing epileptiform discharges (9/93) or ruling in (4/93) or out (21/93) NCSE as the cause of coma or confusion. One EEG was misleading as it showed epileptiform discharges in a patient without a history of seizures but the correct diagnosis of stroke was evident from history and the CT-scan.

Conclusions: Our data suggest that, when properly ordered, emergent EEG is an efficient tool to diagnose epileptic disorders, and to rule out NCSE. Better clinical assessment of a possible first seizure is probably needed to increase its yield. Further study is required to define criteria to select patient at risk of NCSE.

2.042

THE VALUE OF SCALP SPIKE FREQUENCY AS AN EEG MARKER OF EPILEPTOGENESIS IN TEMPORAL NEOCORTEX IN PATIENTS WITH MTLE

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Rationale: Preoperative scalp spike frequency is a strong predictor of surgical outcome in patients with mesial temporal lobe epilepsy (MTLE). It is presumed that scalp spike frequency likely reflect the extent of seizure progression from mesial to lateral temporal cortex. Therefore, patients with frequent scalp interictal spikes are associated with poor surgical outcomes. However, evidence supporting this hypothesis is largely lacking. The objective of our study is to determine the value of scalp spike frequency as a potential EEG marker in gauging the extent of epileptogenesis in temporal neocortex in patients MTLE.

Methods: We recorded simultaneously scalp and intracranial EEG spikes using 26 channels of scalp EEG with sub-temporal supplementary electrodes and 46 to 98 channels of intracranial EEG in 5 patients with medically-intractable temporal lobe epilepsy. Subdural electrodes were implanted extensively on the anterior through mid-temporal lobe. The scalp and intracranial interictal spikes were analyzed for their location and frequency during the first-hour sleep on the 1st day of intracranial study. The intracranial EEG correlates of scalp EEG spikes were then determined.

Results: Mesial temporal seizure onset was recorded in all the 5 patients. A total of 462 ECoG interictal spikes were identified in mesiobasal temporal cortex, and none of these ECoG spikes were recordable on scalp EEG. A total of 1639 ECoG spikes were identified in the lateral temporal neocortex with or without mesiobasal spiking source and only 117 of these ECoG spikes (8%) were recordable on scalp EEG. The percentage of ECoG spikes recordable on scalp EEG is dependent upon their cortical source area and synchrony, and is significantly variable among the 5 patients.

Conclusions: Basomesial temporal spikes need recruiting sufficient amount of lateral temporal cortex in order to be recordable on the scalp EEG. While scalp interictal spike mainly correlates with the spiking source in temporal neocortex, scalp spike frequency may not reflect the frequency of ECoG spikes in temporal neocortex. Therefore, ECoG spike frequency is more reliable than scalp spike frequency in gauging the severity of epileptogenesis in temporal neocortex.

IMAGE: images/908006_A.jpg

Fig 1: 3-D visualization of subdural electrodes obtained from co-registration of post-implant CT and presurgical MRI. Note the extensive electrode coverage of the left baso-mesial, anterior, and infero-lateral temporal cortex. Standard subdural electrodes employed in this study including one 4x8 left mid temporal grid (LMT1-32), one1x8 left anterior temporal strip (LAT1-8), and one1x4 left inferior temporal strip (LIT1-4). The important electrodes that are necessary for identification of all subdural electrodes are indicated in the schematic figure in the right panel. For right temporal lobe implantations grid contact numbering (RMTG 1-32) begins anterior and inferior, rather than posterior and inferior.

IMAGE: images/908006_B.jpg

Fig 2: Simultaneous scalp and intracranial EEG recording showing heterogeneous cortical interictal spikes in patients with left temporal lobe epilepsy. Only a few cortical spikes with sufficient source area and synchrony generated scalp interictal spikes. LOF: left orbital frontal; LATS: left anterior temporal strip; LITS: left inferior temporal strip; LMTG: left mid-temporal grid.

2.043

THE STABILITY OF SPIKE COUNTS IN CHILDREN WITH INTERICTAL EPILEPTIFORM ACTIVITY

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Rationale: Little is known about the stability of spike counts in children with epilepsy. Before interpreting assessments of spike frequency in patients with interictal epileptiform activity, it is important to know whether this is a stable or variable measure. Knowledge of the natural variations in spike frequency may bear on interpretation of maneuvers such as attempted pharmacologic suppression of spikes and help avoid mistaking natural variation for a drug suppression effect. We investigated the night-to-night variation in spike frequency by comparing the spike counts during sleep in children undergoing 48-hour ambulatory EEG recording, comparing spike frequency on the first night to that of the second night.

Methods: We analyzed twelve 48-hour ambulatory EEGs performed at Children's Hospital Boston between August 2009 and June 2010. Studies without spikes, studies during which seizures occurred, or studies that contained artifact that precluded accurate spike counting were excluded. No child's antiepileptic drugs were adjusted during the recordings. When distinct spike foci existed in the same child, these were counted separately. In order to compare comparable sleep segments, we visually counted all spikes occurring during the first night of the recording in the first 20 minutes after the occurrence of the first sleep spindle that appeared during evening/nighttime sleep. The first night's count was compared to the spike count obtained during the second night's sleep during a 20-minute segment defined by the same method.

Results: 17 separate spike foci were counted in 12 children (age range: 3-19 years; mean: 8 years). The firing rate for 7 spike foci increased from the first night to the second night, decreased for 9 foci, and did not change for one focus. The mean absolute percentage change between nights was 23.7% (S.D. = 14.8, range: 0-60%). The coefficient of variation (standard deviation/mean) was 0.62 suggesting moderate variability. The intraclass correlation coefficient was 0.51, also suggesting significant variability (the value would be 1 if measurements were completely stable between nights).

Conclusions: In our group of 12 children with 17 spike foci, significant variability in spike frequency was seen during comparable segments of stage II sleep, despite the lack of intervention (e.g., medication changes) between the two nights. The mean percentage change of 23.7% and high coefficient of variation and intraclass correlation of these measures suggest significant natural variation in this phenomenon. Conclusions regarding observed changes in spike counts in the clinical setting should be made with caution.

2.044

LATERALIZATION OF GENERALIZED SPIKES AFTER CORPUS CALLOSOTOMY

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Rationale: Corpus callosotomy is aimed to disrupt inter-hemispheric propagation of epileptic activities generating tonic, atonic or secondarily generalized seizures. Section of corpus callosum often results in dramatic changes in interictal spikes, for example desynchronization or lateralization of bilateral spikes. Recent case reports suggested that such post-callosotomy changes of epileptiform discharges may uncover epileptic foci in one hemisphere which secondary leads to respective epilepsy surgery. The purpose of this study is to reveal the relationship between the interhemispheric latency of bisynchronous spikes and post-callosotomy changes of those spikes.

Methods: The study included 6 patients with intractable generalized epilepsy (3 cryptogenic and 3 symptomatic cases) who had infantile or early childhood onset of disease and received one-stage total corpus callosotomy for the alleviation of seizures. The age at surgery was ranged from 1 year 5 month to 15 years. Inter-hemispheric latency of interictal spikes were calculated in the pre-operative EEG, and compared with post-operative EEG.

Results: Pre-operative EEG was characterized by generalized or bihemispheric multi-focal spikes in all cases. Post-operatively, spikes were lateralized to one hemisphere in 2 and became bilaterally independent in 2 cases. No notable changes were found in the remaining 2 cases. In the 2 cases with post-operative lateralization, pre-operative spikes were characterized by "one-way propagation" of spikes, i.e. spikes propagating from one hemisphere to the other hemisphere, and lateralization occurred to the hemisphere with leading spikes. Inter-hemispheric latency was generally within 20 ms in all cases. There was no clear association of the latency and the pattern of propagation to post-operative outcome.

Conclusions: Generalized spikes with one-way propagation pattern results in lateralization of the spikes to the leading hemisphere after corpus callosotomy. This type of post-operative EEG changes may reveal epileptogenic foci in one hemisphere post-operatively.

2.045

CONSCIOUSNESS AND SEIZURE CHARACTERISTICS IN ADULTS WITH RECURRENT ABSENCE STATUS AND GENERALIZED EPILEPSY

P. S. Mireles and C. A. O'Donovan (Wake Forest University Baptist Medical Center, Winston Salem, NC)

Rationale: Alteration of consciousness and attention can show wide degrees of heterogeny between patients with absence seizures thought to be due to similar generalized epilepsy syndromes. Atypical electroclinical characteristics are associated with refractoriness to AEDs and persistence into adulthood. We describe three adult patients with frequent and prolonged generalized epileptiform discharges and absence seizures with different manifestations of seizure occurrence and alteration of consciousness.

Methods: Three adult patients with recurrent absence status as predominant seizure type and prolonged runs of generalized epileptiform discharges during VEEG were identified. Seizure characteristics and frequency, EEG features as well as response to drug therapy were reviewed.

Results: Patient 1 had absence seizures for one year as a child which responded to treatment but recurred at 50 years and are currently refractory. Patient 2 who developed seizures later in life experiences bouts of absence status terminating in convulsions at no other time but once per year. Patient 3 with adult onset epilepsy has ictal patterns of generalized delta and theta and some focal features on EEG. His complaints are of epsiodic amnesia as his main symptom with evidence of ability to complete battery of complex neuropsychological tasks during prolonged ictal periods documented by VEEG.

Conclusions: Lack of correlation between epileptiform patterns on EEG, altered awareness and seizure rates in these adult patients is further evidence of the heterogenous nature of generalized epilepsy syndromes with absence seizures. Detailed neurophysiological and hemodynamic imaging studies into absence seizures in these older patients may provide further insight into the pathophysiology of intractability and persistence into later life.

2.046

NEONATAL SEIZURES: ICTAL EEG CHARACTERISTICS

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Rationale: There is a high incidence of mortality and morbidity associated with neonatal seizures (NS). EEG plays an integral part in accurately diagnosing NS and the background helps prognostication. The characteristics of the ictal EEG may also contribute to prediction of outcomes, understanding of pathogenesis and tailoring of investigations.

Methods: We analysed the ictal EEG in 160 NS in 43 babies, captured during a standard VEEG recording and correlated it with outcomes.

Results: Of the 160 NS, 61 had clinical correlates (electroclincal szs:ECSz) and 99 were electrographic only (ESz). Overall 40% of NS arose from sleep, 31 from wakefullness and 28 were undetermined; ECSz occurred more frequently from wakefullness. The highest frequency and maximum amplitude of the ictal EEG was significantly higher (p=.0075 and .00001) during the ECSz compared to ESz, with no difference in onset frequency, or mean duration of NS.

Table 1 shows NS onset from different areas: temporal being most frequent with frontal and paracentral following.

As shown in Table 2, ESz tended to remain focal, regional and hemispheric more frequently than ECSz

Mortality was 1/11 with babies with ECSz only, 2/13 in those with both and 6/19 in those with ESZ only. Babies with ECSz had better background EEG and outcomes than those with ESz.

Conclusions: Conclusions: Ictal EEGs in ECSz have a higher maximum frequency and amplitude and tend to spread to a larger area of the brain than in ESz. Babies with electroclinical dissociation have poorer background EEG scores, more frequent neurodevelopmental sequelae and higher mortality. NS start most frequently in the temporal, followed by the frontal and paracentral regions. This suggests we may need to reconsider ideal montages for amplitude intergrated EEG.

References:

Nagarajan L et al. Neurodevelopmental Outcomes in Neonates With Seizures: A Numerical Score of Background Encephalography to Help Prognosticate. J Child Neurol. 2010: doi 10.1177/0883073809355825

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Seizure onset

IMAGE: tables/901493_T1.jpg

Seizure spread

IMAGE: tables/901493_T2.jpg

2.047

THE EPILEPSY PHENOME/GENOME PROJECT (EPGP): INFORMATICS TOOLS AND WORKFLOW FOR PROCESSING ELECTROENCEPHALOGRAM (EEG) DATA

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Rationale: EEG data are collected on EPGP study subjects to confirm epilepsy diagnosis and classification, and facilitate the investigation of genetic contributions to specific EEG abnormalities and phenotypic characteristics. The challenges faced in creating a platform to collect these data include the selection of tools to view and de-identify multi-vendor format EEGs, efficient electronic transfer of EEG files, and development of web-based tools to collect accurate phenotypic data and to facilitate the EEG Core Review process.

Methods: Clinical site study coordinators upload each subject's EEG to a secure FTP server, and each EEG is then examined and archived by

the EPGP Data Manager and converted to Persyst (Persyst Development Corp, Prescott, AZ) format in the process. Newly developed web-based tools allow neurologists at each site to collect phenotypic data and enable the EEG Core members to review and score the EEG data collected. Following clinical site submission and review of EEG data, Initial Inclusion Review is performed by one EEG Core member, Final Review by two independent EEG Core members, and Final Consensus Review by three or four EEG Core members.

Results: 755 EEGs have been uploaded to date, of which 680 are initial inclusion EEGs and 75 are supplemental EEGs. A total of 189 EEGs are awaiting evaluation by the clinical site neurologist and 563 EEGs have been, or are in the process of being, reviewed by the EEG Core members. 35 EEGs did not meet EEG inclusion criteria or were deemed technically inadequate on EEG Core Initial Inclusion Review and 14 EEGs did not meet EEG inclusion criteria based on Final Consensus Review. To date, 289 eligible EEGs have been phenotyped via Final Consensus Review (215 digital), of which 210 (73%) had modifications made to EEG phenotypic details during Core Review. The majority of these modifications were minor phenotyping disagreements between site reviewers and Core reviewers, which were adjudicated on Final Consensus Review.

Uploading digital EEGs to the FTP server was very efficient. A one hour EEG can be archived (i.e. converted to Persyst format) and de-identified in less than 45 seconds using Persyst Insight II®. Some digital EEGs were not compatible with Persyst Insight II® and had to be viewed using their native browsers.

Conclusions: The rigorous review process likely improves the accuracy of EEG phenotyping. The customized EPGP EEG web tools provide a feasible model for use in other epilepsy studies. We anticipate that the collection of phenotypic EEG data using these semi-automated processes will help to identify the genetic contributions to specific EEG abnormalities in EPGP and future epilepsy studies.

2.048

ASSESSMENT OF TRAINEE EXPERTISE IN INTERPRETATION OF NEONATAL EEG WITH THE USE OF INTER-READER RELIABILITY METHODS

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Rationale: Methods of assessment of fellowship training in clinical neurophysiology often poorly duplicate clinical practice and do not explicitly account for disagreements in expert interpretation. The purpose of this study was to use inter-reader reliability methods to assess expert and trainee agreement in interpretation of a sample of EEG recorded from term neonates.

Methods: Two board-certified experts and two trainees (A=at end of fellowship, B=beginning of fellowship) independently ranked 1 hour long EEGs that were recorded from term infants with presumptive hypoxic-ischemic encephalopathy between 1-3 days of life according to presence of interictal epileptiform discharges, presence of epileptic seizures, and a 4 point encephalopathy severity scale. Inter-reader agreement and reliability, the latter measured via the kappa statistic, were measured for each category across the experts. The 95th confidence limit of kappa was selected for a threshold level by which the inter-reader reliability of each trainee was measured.

Results: Agreement rates/reliability(reliability 95th confidence interval) between the two experts was IED=0.780/.560(0.283-0.837), seizures = 0.940/0.694(0.416-0.971), overall severity = 0.800/0.722(0.571-0.873). Reliability of Fellow A exceeded the lower confidence limit for all 3 criteria; reliability of Fellow B exceeded the threshold value in only seizure detection. The lower confidence limit of kappa varied linearly with the number of studies.

Conclusions: Inter-reader agreement and reliability in interpretation of conventional multichannel EEG of term neonates is high (but less reliable in the designation of pathophysiological interictal epileptiform discharges). The use of fewer studies in this technique is feasible. Reliability measurements may provide a practical and clinically relevant means of interim and final fellowship assessment.

2.049

SCALP TEMPORAL POSITIVE SHARP WAVES MAY ORIGINATE FROM THE MESIAL TEMPORAL CORTEX

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Rationale: Scalp recorded interictal epileptiform discharges (ied) typically appear as negative polarity sharp transients. They are generated on superficial layers of the cortex by the summation of extracellular EPSPs. A passive return current generates a positive pole equivalent in the deeper layers of the cortex: this can be also recorded by scalp electrodes at some distance from the negative maxima as a lower amplitude positive sharp transient. The identification of the positive maximum of an ied may define the orientation of the dipole and help in localizing it. Some scalp recorded ieds exhibit a prevalent positive polarity without evident negative maxima; other ieds show an initial low amplitude positive component preceding a subsequent prevalent negative sharp transient. These positive scalp ieds may originate from a cortical source with orientation rotated by ~180 degrees relative to that of the hemispheric gyral surfaces, i.e. for example, the mesial inter-hemispheric, mesial temporal and the internal opercular cortices. We have identified EEG recordings presenting these positive waves and looked for evidence indicating a source in any of these regions.

Methods: A retrospective chart review of the Epilepsy Program of our Hospital identified at least 6 patients (pts) with positive scalp temporal discharges. On all pts seizure history, brain MRI and video-EEGs were obtained: 2 pts were implanted intracranial electrodes. 3 pts had a Magneto encephalogram (MEG).

Results: Seizure semiology of all pts indicated mesial temporal lobe seizures with staring and orofacial/manual automatisms. MRI showed temporal lobe abnormalities in 4 pts (with mesial temporal sclerosis (mts) in 3 pts (see MRI image)and cavernoma in 1 pt). In the remaining 2 pts no temporal lobe lesions were seen. EEGs showed positive sharp transients over the temporal and parietal electrodes in 4 pts (see EEG traces), more pronounced and persistent in the 3 pts with hippocampal atrophy. In 2 pts typical negative ieds in the temporal electrodes were preceded by an initial low voltage positive component. Intracranial recordings in 2 patients confirmed the presence of parahippocampal discharges. MEG was performed in 3 pts and showed basal or mesial temporal epileptiform discharges.

Conclusions: On a theoretical basis, ieds originating from the mesial temporal cortex may be recorded by ipsilateral scalp electrodes as low voltage sharp transients of positive polarity. We have provided experimental data of such low voltage positive polarity discharges in the ipsilateral lateral chain of electrodes in patients with evidence of

mesial temporal lobe epileptiform activity. These positive discharges are more pronounced in pts with ipsilateral hippocampal atrophy. Some pts exhibit scalp temporal ieds with an initial low voltage positive component and this may correspond to an initial source over the mesial temporal cortex.

IMAGE: images/905232_A.jpg

IMAGE: images/905232_B.jpg

2.050

INTER-RATER VARIABILITY IN QUANTIFICATION OF EPILEPTIC SPIKES; A SPIKE-BY-SPIKE ANALYSIS

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Rationale: Epileptic spikes have been used as a surrogate marker of abnormal brain electric activity; however, spikes vary in morphology, distribution, duration, and amplitude. At times identification of individual spikes may vary among electroencephalographers. Using EEGs in children with Benign focal epilepsy of childhood with centrotemporal spikes (BECTS), we studied variability in spike identification between two electroencephalographers. Such spikes were chosen for analysis, as epileptic spikes in BECTS have characteristic morphology and distribution that are readily identifiable.

Methods: This was part of a study on clinical and electrographic features of children with BECTS, approved by the institutional review board at Children's Hospital Boston. We analyzed routine awake and sleep EEG studies of randomly selected 5 children with BECTS (3 boys, 2 girls, age range: 7-11 years). For all studies, the first 5 minutes of stage II sleep were analyzed, where there were potentiation of centrotemporal spikes without significant contamination by movement or slow waves. Two blinded fully-trained electroencephalographers (Rater A and Rater B) marked each individual spike in the EEG segments, and a third blinded independent evaluator compared the results of spike markings. Spike identification by each rater was assessed by the evaluator, on a spike-by-spike basis, as well as comparing total number of identified spikes.

Results: A total of 1500 seconds were analyzed over the 5 patients (300 seconds per patient). Rater A marked a total of 394 spikes (range 22-234 spikes per patient, mean 79+/-88 spikes), and Rater B marked a total 452 spikes (range 40-239 spikes per patient, mean 90+/-84 spikes). The difference in total of spikes between raters was 58 (13% of all spikes). For per patient, the difference between raters ranged 5-22 spikes per patient (2-50% of spikes, mean 12+/-7%). For spike-by spike analysis, discordance of identification between raters totaled 105 spikes (23% of all spikes). This ranged 13-27 spikes per patient, (5-55% of spikes, mean 37+/-19%). Major discordance was seen in spikes with less typical features for BECTS, such as 1) less typical morphology, 2) low amplitude, 3) less typical spread in distribution.

Conclusions: Accurate identification of epileptic spikes remains a very challenging task. Even in BECTS, a relatively homogeneous epileptic syndrome with specific characteristics of epileptic spikes, our study found a great variability in identification of spikes. This was more emphasized when assessing on a spike-by-spike basis, while such difference became diluted when assessing total spike quantity only. Factors causing more variability in spike identification may need to be further delineated with future studies. Automated identification of individual epileptic spikes may be even less accurate compared to identification by trained electroencephalographers. Such factors associated with difficulty in accurate spike identification are significant for clinical care and research studies, as well as development of automated spike detection algorithms.

2.051

LONGER INTERMITTENT PHOTIC STIMULATION INCREASES PHOTOPAROXYSMAL RESPONSE YIELD

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Rationale: Despite the widespread clinical use of intermittent photic stimulation (IPS), EEG laboratories conduct the procedure with a high degree of variability. No study has identified the range of flash stimulus duration required to achieve a photoparoxysmal response (PPR). The aim of this study was to determine the range of IPS required to produce a PPR to aid in developing a standardized protocol.

Methods: A retrospective analysis of the EEGs from the Division of Pediatric Neurology at Boston Medical Center between 2005 and 2009 yielding a PPR was performed. In 2007 the IPS protocol was changed from 5 second to 10 second flash trains, and data from before and after this protocol change were collected for comparison. All participants 30 years of age or younger were included. All EEGs were independently reviewed by two blinded epileptologists and data on PPR were collected, including time of onset, duration, distribution, morphology, presence of a driving or a photomyogenic response, and evidence of a clinical seizure. Discrepancies between the two reviewers were discarded. The morphology and distribution of the PPR were categorized using the Waltz 4 stage grading system (Waltz et al., Electroencephalogr Clin Neurophysiol 1992;83(2)138-45). Summary statistics were produced for time of PPR onset, and these were compared among the 4 grades of PPR.

Results: Of 175 reports identified, 117 were excluded due to either absence of PPR, frequent background epileptiform activity, or presence of only a driving response. Among the remaining 58 studies, 245 frequency trains produced a PPR, 33% from the 5 second flash protocol and 67% from the 10 second protocol (table). Overall mean PPR onset was 2.33 seconds (range 0.08 to 9.54). Mean PPR onset was not significantly different among individual flash frequencies ($p=.18$). Mean PPR onset for the 5 second trains (1.44 seconds ±1.50) was significantly different from the 10 second trains (2.67 seconds ±2.51, $p<.001$). Within the 10 second protocol 30 of 165 PPRs (18%) began at least 5 seconds after IPS onset (figure). Of the 40 studies with 10 second flash trains, 7 (18%) would have been misclassified as negative if stimulation only lasted 5 seconds, including two Grade III (5.1 to 7.7 seconds) and five Grade IV (5.6 to 7.6 seconds).

Conclusions: These findings support an IPS protocol of flash trains lasting at least 8 seconds, a duration which would have yielded positive findings in all studies. Although a small percentage of PPR began after 8 seconds, all of the studies in which this occurred had earlier PPR in other frequencies. The majority of the PPRs detected between 5 to 10 seconds were Grade IV, which are most closely associated with a diagnosis of epilepsy. Our study had several limitations, most importantly our protocol only included frequencies up to 25 Hz and could have missed PPR brought out by higher frequencies. In summary, the modification of existing protocols to include longer flash trains

would likely increase the yield of IPS by 15 to 20%, and could improve the management of patients with epilepsy.

IMAGE: images/908335_A.jpg

IMAGE: images/908335_B.jpg

2.052

INTERICTAL SPIKE AND HFO OCCURRENCE FREQUENCY IN TUMOR-RELATED REFRACTORY EPILEPSY

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Rationale: High frequency oscillations (HFOs) have been linked as a biomarker for seizure genesis. Determining the spatial and temporal relationship of HFO to spike frequency in patients with tumor-related refractory epilepsy may further clarify the epileptogenic onset zone in these patients.

Methods: Three 10-minute interictal intracranial (IC) EEG samples were taken from six patients with tumor-related refractory epilepsy undergoing 2-stage surgery. IC-EEG samples were taken daily roughly at the same time of the day, during awake, resting phase, and >6 hrs following a seizure. Automatic spike detection software (Stellate Systems) was used to identify the individual spikes. Each file was manually corrected by a single EEGer to remove artifacts and manually mark the spikes missed by the software. Each intracranial electrode (ICE) location was blindly identified by type as tumoral (T), peritumoral (PT), or non-tumoral (N) based on preoperative and post-implantation neuroimaging. In addition, each ICE was labeled by zone as seizure onset (SO), seizure spread (SS), or neither (N). Seizure onset and spread together were defined as the epileptogenic zone.

Each IC-EEG sample was separately marked by a single EEGer for HFOs. EEG was sampled at 200Hz or 1,000Hz and filtered with a high-pass filter of 50Hz. Automatic computer program analysis was performed in Matlab (MathWorks) to calculate the frequency at which HFOs and spikes occurred at each ICE. Two-hundred milliseconds of data were searched on either side of a marked HFO to look for concurrent spike activity (SHFO). Data analysis included comparing spike frequency, HFO occurrence, and SHFO frequency to both electrode type and zone using ANOVA with subject blocking and Tukey tests as needed. Analysis of frequency and Chi-square of electrode type by electrode zone was also preformed.

Results: A total of six patients were included in the analysis and the number of ICEs ranged from 41 to 96. ANOVAs looking at electrode zone with spike, HFO, and SHFO were significant for HFO ($p<0.0001$) and SHFO ($p<0.0001$). Post-hoc comparison of means by Tukey tests showed significant positive differences for seizure onset zone to spread or neither, but not when comparing spread to neither. There was no relationship for spike and electrode zone. ANOVAs looking at electrode type were significant only for HFO, with PT versus T and N being significant. Total percentages of electrode type by electrode zone showed onset electrodes outside of the tumor or peritumor region half of the time.

Conclusions: Electrodes with a high frequency of spiking activity are not necessarily good predictors of the seizure onset zone, while electrodes with a high frequency of HFOs and HFOs with concurrent spikes, especially outside the tumoral region, are good predictors of the seizure onset zone.

2.053

THE DIAGNOSTIC UTILITY OF ROUTINE (20-40 MINUTES) ELECTROENCEPHALOGRAM IN ELUCIDATING THE ETIOLOGY OF ALTERED MENTAL STATUS NOT OTHERWISE SPECIFIED

Merry Chen, C. Sinsioco, N. Sethi and G. Solomon (New York Presbyterian Hospital, New York, NY)

Rationale: Patients with altered mental status not otherwise specified (AMS NOS) are frequently referred for routine (20-40 minute) electroencephalogram (EEG). The intention is to rule out seizures specifically non-convulsive seizures (NCS) as the etiology of AMS. The EEG may also suggest a structural or metabolic/ toxic cause of AMS and thus helps guide further diagnostic work up. The aim of our study was to determine the diagnostic utility of the EEG to clarify and differentiate possible causes of altered mental status.

Methods: All consecutive routine/portable EEGs of adult inpatients (= or > 18 years of age) with the diagnosis of AMS, change in mental status or encephalopathy over a nine-month period (July 2009 - March 2010) were reviewed by a board certified electroencephalographer and clinical neurophysiology fellows. EEGs were reviewed for 1. Slowing - focal vs. diffuse, 2. Presence or absence of epileptiform features (sharp waves or spike wave discharges), 3. Special features- triphasic waves, periodic lateralized epileptiform discharges (PLEDS), generalized periodic epileptiform discharges (GPEDS) and bilateral independent periodic epileptiform discharges (BIPLEDS). In addition, we correlated the neuroimaging findings in patients with focal abnormalities on EEG. EEG records of patients who underwent long-term video EEG monitoring were reviewed to determine whether it aided further diagnostic assessment and plan.

Results: A total of 122 EEG studies with a diagnosis of AMS were referred to the lab during the above nine month time period. Overall, there were 15 (12.3 %) normal EEGs and 107 (87.7%) abnormal EEGs. Among the abnormal EEGs, 94 (87.8%) showed slowing. Diffuse slowing occurred in 70/94 (74.5%) while focal slowing occurred in 24/94 (25.5%). Epileptiform discharges were seen in 13 (10.6%) of all EEGs reviewed, of which 12 (92.4%) had focal epileptiform discharges. No definite seizures were recorded in any of the EEGs reviewed. Triphasic waves were present in 22 (18%) of all EEGs reviewed. PLEDS were seen in 2 EEGs while none had GPEDS or BIPLEDS. Among the patients who had focal slowing on EEG, 18 out of 24 (75%) had a concordant abnormality documented on neuroimaging. Among the patients who had focal epileptiform abnormalities on EEG, only 5 out of 12 (41.7%) had a corresponding abnormality on neuroimaging. 10 patients underwent further prolonged video-EEG monitoring. Video EEG monitoring suggested the possibility of nonconvulsive status epilepticus in one patient of these 10 patients.

Conclusions: Routine/portable EEG studies are useful in the diagnostic workup of patients with altered mental status. The majority of EEGs of patients with altered mental status showed slowing. Triphasic waves, epileptiform discharges, and PLEDs were seen in a minority of the EEGs. EEG has a high sensitivity but low specificity in elucidating the etiology of AMS.

2.054

P300 IN TEMPORAL LOBE EPILEPSY PATIENTS

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Rationale: Cognitive dysfunction in patients with epilepsy may stem from neurophysiological changes related to seizure or to anti-epileptic drugs (AEDs). Previous studies have examined P300 in patients with epilepsy to evaluate cognitive disturbances. However, the effects of epilepsy or AEDs on P300 activity still remain controversial. We examined alteration in P300 activity in patients with temporal lobe epilepsy (TLE).

Methods: We examined 14 TLE patients (six females). The mean age was 33.0±12.9 (20 - 50 years). The mean age of onset was 22±12 (3-25 years). Six of 14 were seizure free for more than 20 months. Seven patients took none or one AED, three patients two AEDs, and four patients more than three AEDs. Control data was collected 14 age-matched healthy comparisons (seven females, all right handed).

P300 were elicited by a series of pure-tone (1,000 and 1050 Hz). The tones were presented at a rate of one trial per 500 ±50 ms in a random sequence with the 1050 Hz (rare, target) pure-tone occupying 20% (200 times) and 1000 Hz (frequent, non target) pure-tone occupying 80% (200 times) of the total beeps. The P300 was recorded from four midline electrodes (Fz, Cz, Pz, Oz) and EOG. At least 20 responses for rare stimuli were analyzed in each session. We evaluated the peak amplitude, mean amplitude and peak latency at Fz, Cz and Pz between 250 and 450 ms after onset of stimuli.

ANOVA was used to compare P300 parameters between TLE and healthy participants.

Clinical parameters (age of onset, numbers of AEDs, seizure frequency) in patients with TLE and P300 parameters were compared using Spearman's correlation coefficient by rank test.

Results: Patients with TLE patients showed significantly reduced mean and peak P300 amplitudes compared to healthy comparisons. ($p<0.001$) There was no significant difference in peak latency between TLE and healthy comparisons.

The patients who had no seizure for more than 20 months showed a trend of even lower amplitudes compared to patients whose seizure were not controlled.

In TLE patients, numbers of AEDs or age of onset were not related to P300 parameters.

Conclusions: Patients with TLE showed significantly lower P300 amplitudes than healthy participants. Furthermore P300 amplitudes were affected in TLE patients in TLE patients even after seizure remission for more than 20 months.

IMAGE: images/901611_A.jpg

2.055

CHRONIC USE OF FELBAMATE INCREASED RIPPLES IN EEG

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Rationale: Felbamate is an inhibitor of glutamate receptor of NMDA type and a very effective anticonvulsant for intractable complex partial seizure. It is estimated that approximately 70,000 patients have had it prescribed for seizure control. However, there is no previous report of chronic felbamate effect on electroencephalogram. Relation between AED withdrawal and high-frequency activity was suggested by some studies, but clinical implication of an individual drug has not been discussed. Knowing that scalp EEG may detect high-frequency oscillation (HFO) during sleep state in the frequency range up to 140 Hz (Kobayashi, Epilepsia 2010), this presentation speculates three steady seizure-free cases of chronic felbamate therapy that demonstrated findings of enhanced high-frequency oscillation in scalp EEG.

Methods: Three patients (patient #1, #2, and #3) were referred to the Bronson Epilepsy Outpatient Clinic with a history of intractable complex partial seizure disorder but seizure free for more than 10 years by established felbamate monotherapy, and had recent EEG studies with hope of drug termination. These EEGs were routine 10-20 system scalp recording in awake and sleep state with a sampling frequency of 1000 Hz using Nicolet system.

Results: A common feature of the EEGs, of the three seizure-free patients with felbamate, was sustained gamma ripple with bilateral frontotemporal distribution during the sleep state. The patient #1: 27 year old man with history of hydrocephalus and shunt placement in the right hemisphere. He has been on felbamate (2800 mg/day) since it was released in 1994. EEG showed 80-150 Hz bi-frontotemporal ripple sustained during sleep state. The patient #2: 41 year old man with history of intractable seizure, treated with felbamate (400mg bid) for 12 years and no seizure in the past 10 years. EEG showed intermittent 125-150 Hz bilateral frontotemporal ripple with left side preponderance. Interictal discharges were seen in the right posterior temporal lead. The patient #3: 56 year old man with frontal lobe seizure originating from the right frontal neocortex with felbamate (600 mg bid). EEG showed 80-100 Hz bilateral frontotemporal ripples.

Conclusions: Scalp recording has limitation of recordable frequency range up to 140 Hz as ripple. Enhanced bilateral frontotemporal high-frequency ripples were the common finding in the sleep state EEGs of these three patients who have received steady dose of felbamate and had seizure-free state. The distribution of these ripples was bilateral frontotemporal regardless of lateralization of a primary epileptogenic focus. The findings may suggest that chronic use of felbamate maintains high-frequency oscillation (HFO) in the frontotemporal neocortex. In previous studies (Staba, et.al., 2007), it was suggested that high frequency ripple discharges may represent protective activity of the synchronous GABA inhibitory mechanism. Felbamate inhibitory mechanism may have parallel features of chronic NMDA receptor inhibition and GABA receptor accentuation. The limitation of the study is small number of seizure-free steady state cases by felbamate.

2.056

HEAD-SURFACE EEG GEOMETRY OF FOCAL INTERICTAL EPILEPTIFORM TRANSIENTS (FIET)

Fumisuke Matsuo (University of Utah Medical Center, Salt Lake City, UT)

Rationale: Head-surface EEG can be configured to display voltage gradient change in a computer-generated cartoon image sequence. FIET peak movement in space domain is easily appreciated and suggests propagation within the epileptogenic neuron matrix. Such a review-analysis is too impressionistic to generate a useful summary of FIET geometry. A simple protocol to capture spatiotemporal data from time-domain peaks in polygraphic EEG, and plot them in a series of head-surface maps, was applied to a randomly chosen set of FIET in this exploratory study.

Methods: One representative FIET was chosen from each of 110 consecutive EEG records in a 2-year period. A total of 23 head-surface electrodes included the 10-20 System and 2 basal pairs (zygomatic and mastoid). FIET, less than 150 ms in duration, were ranked by conventional waveform criteria. The top 50 FIET were examined in common average derivations at highest time resolution. The operator would follow polygraphic channels, manually advancing cursor at 5-ms interval (t), and plot the FIET peak (at most one per channel) onto a STMap panel (18 head-surface maps, designed as modified stereographic projection), covering a period of 90 ms, time-coded from -12t through 5t with 0t set at the dominant peak. STMaps were classified according to the pattern of peak movement.

Results: The primary finding was that the longer interpeak latency, the more distant, space domain separation of component peaks. FIET formed 2 contrasting groups, one, 40 FIET with local peak components only, and the second, 10 FIET, with distant as well as local peak components. Local peak components revealed no movement (defined as no peak separation longer than 10 ms) in 17 of 40 FIET in the first group. FIET with distant peak components revealed multiple clustering and latency variation, suggestive of interlobar and/or interhemispheric propagation. FIET duration did not differ significantly between 2 groups.

Conclusions: Local peak components are what the clinical electroencephalographer recognizes to infer a localized epileptogenic matrix, conventionally represented by the dominant peak, while FIET peak movement to distant locations is suggestive of secondary epileptogenesis, and refractoriness to treatment. The significance of peak movement near the dominant peak, seen in 23 FIET, is to be further investigated. The dominant FIET peak more often belonged to the basal hemisphere, reflecting a larger number of FIET of presumed temporal lobe origin. Geometric examination of FIET peak components may help better define the clinical neurophysiology of epileptogenesis, and its natural history.

2.057

SUPPRESSION OF INTERICTAL EPILEPTIFORM DISCHARGES BY LEVETIRACETAM DURING VIDEO-EEG MONITORING

Jeremy Moeller, C. W. Bazil and R. G. Emerson (Columbia Comprehensive Epilepsy Center, New York, NY)

Rationale: Levetiracetam (LEV) is one of the most commonly used newer anti-epileptic drugs. Previous studies have shown that LEV suppresses generalized discharges in idiopathic generalized epilepsy, and there has been one published report of the suppression of interictal epileptiform discharges (IEDs) in patients with frequent focal discharges. However, we are not aware of any published studies examining the effect of LEV on IEDs during inpatient video-EEG monitoring.

Methods: We reviewed the records of patients with definite epilepsy who underwent video-EEG recording at Columbia Comprehensive Epilepsy Center between January and April 2010. Patients were included if they were: (a) withdrawn from LEV to provoke a seizure; (b) started on LEV; or (c) had a significant change in LEV dosage during monitoring. Clipped samples were made of each patient's daily 24-hour video-EEG files (5 minutes of every hour). These clipped files were reviewed by two blinded readers (CWB, RGE). All IEDs were identified and counted, and mean IED density (IEDs/hour) was calculated for each 24 hour period. IED density while each patient was taking LEV was compared to IED density while each patient was not taking LEV, or taking a reduced dosage.

Results: We identified 10 patients with epilepsy who had significant changes in LEV dosage during video-EEG monitoring. Two patients had idiopathic generalized epilepsy, and 8 patients had localization-related epilepsy (five with temporal lobe epilepsy, two with frontal lobe epilepsy, and one with multifocal epilepsy). 4 patients had LEV tapered and then restarted, 2 patients had LEV discontinued, and 2 patients had LEV introduced during recording. The remaining two patients had significant changes in LEV dosage, but never completely stopped the medication. In the 8 patients where spike density "off LEV" could be compared to spike density "on LEV" 5/8 had a 16-92% decrease in IED density while taking LEV and in one patient, LEV appeared to completely suppress IEDs. In two patients where LEV was never completely stopped, an increase in LEV dosage resulted in almost complete suppression of IEDs. In one patient (with multifocal epilepsy) the introduction of LEV appeared to increase spike density, and in one patient, LEV did not change spike density.

Conclusions: Levetiracetam suppressed interictal epileptiform discharges in the majority of patients during inpatient video-EEG monitoring, including almost complete suppression of discharges in 3/10 patients. Levetiracetam has potential to significantly alter the yield of interictal EEG recordings in patients with epilepsy.

2.058

EARLY EEG IN PATIENTS WITH NEW-ONSET SEIZURES: CORRELATION WITH NEUROIMAGING FINDINGS AND SEIZURE RECURRENCE

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Rationale: Well adults presenting to the emergency room (ER) after isolated new-onset seizures are often discharged to the neurology outpatient service for further evaluation. A long waiting time may delay this assessment, possibly resulting in non-diagnostic EEG. The yield of EEG might be improved when performed soon after a seizure. We sought to assess the utility of EEG in these patients within an ER setting, correlating the findings with neuroimaging data and the incidence of recurrent seizures.

Methods: Patients attending the ER from January 2008 to December 2009 with uncomplicated first episodes of unprovoked convulsive seizures were included. All made a complete neurological recovery and underwent 30-minute EEG using a 10-20 international montage prior to being discharged. ER physicians were blinded to the EEG findings. Correlation was made with neuroimaging (either CT or MRI) that was performed based on standard clinical ER protocols and independent of EEG results. Seizure recurrence was assessed during a 12- month period from the time of initial presentation.

Results: 84 patients were included in the study (55 males, 29 females). The mean age was 31.4 years (range 16-61). 30 (35.7 %) had abnormal EEG: 13 patients with lateralized epileptiform discharges, 8 isolated focal slowing, 7 generalized spike-wave discharges and 2 diffuse slowing. The sensitivity, specificity, positive predictive value and negative predictive value of EEG in predicting abnormal neuroimaging were 67%, 60%, 35%, and 85% respectively [OR 4.8 (95% CI 1.2-19.7)] after adjusting for age and sex. In those with lateralized EEG abnormalities and positive neuroimaging, regional concordance between the two was 71.4%. The sensitivity, specificity, positive predictive value and negative predictive value of EEG in predicting 12 month seizure recurrence were 62%, 70%, 27%, 91% respectively [OR 3.6 (95% CI 1.09-11.6)] . Of 66 patients who were not commenced on anticonvulsant medication during the follow-up period, 8 had recurrent seizures, 5 of whom had abnormal initial EEGs at the time of presentation.

Conclusions: The diagnostic yield of EEG in uncomplicated new onset seizures may be improved if performed acutely. It can serve as an additional tool to aid the selection of patients who will benefit from early neuroimaging beyond standard ER protocols. It can be used to stratify patients who are unlikely to have recurrent seizures. Patients with abnormal EEG who are should be closely monitored in the epilepsy clinic.

2.059

THE DIAGNOSTIC YIELD OF AN EXTENDED SLEEP EEG IN ANGELMAN SYNDROME

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Rationale: Angelman syndrome (AS) is a neurogenetic disorder characterized by impairment of neurologic development, poor or no language acquisition, a unique behavioral profile and a wide-based gait with jerky movements. Approximately, 90% of patients with AS have epilepsy and more than 92% of patients have characteristic rhythmic EEG abnormalities Interictal epileptiform discharges (IEDs) consisting of focal, multi-focal or generalized epileptiform discharges are also seen (Dan and Boyd, 2003). In a general epilepsy population, the mean time to the first IED has been shown to be 32.8 minutes during a prolonged outpatient EEG (Losey et al. 2008) and it has previously been shown that abbreviated EEG montages used during polysomnography (PSG) are suboptimal in seizure detection and localization ((Foldvary-Schaefer et al, 2006).The goal of this study was to define the optimal EEG recording (length and montage—full head vs. limited) needed to identify ictal, interictal and benign abnormal rhythms in AS.

Methods: Overnight sleep EEGs in conjunction with overnight PSG from 16 patients with AS between the ages of 3 -16 years old enrolled in the Angelman Natural History protocol study were reviewed. A blinded electroencephalographer reviewed the first hour of each EEG using 6- and 21-channel montages. Data was first reviewed in the 6-channel montage and then in the 21-channel montage at least 72 hours later. Each EEG received a score based on finding found on the EEG. The categories scored included: overall EEG impression, EEG background appearance, presence of an occipital rhythm, rhythmic theta or delta, epileptiform abnormalities, and sleep. A second epileptologist independently reviewed the studies to confirm inter-rater reliability of the scores. After each EEG was scored in the different montages, a chart review was done to identify clinical history of seizures and any previous epilepsy monitoring unit (EMU) admissions.

Results: Although 81% of patients had a clinical history of seizures and were on anti-epileptic drugs (13/16), only 18% had IED and/or ictal discharge on prolonged EEG (3/16).These proportions were similar on both the 6- and 21-lead EEGs. Only 1 of the 18 patients had an admission to the EMU. Both the limited 6-lead EEG and the full 21-lead EEG were able to distinguish benign abnormal rhythms, in particular the diffuse rhythmic delta pattern. There was 100% concordance in identifying rhythmic delta and/or theta patterns. Otherwise, the background abnormalities, presence or absence of sleep patterns, and overall background appearance were often misrepresented on the 6-lead EEG. The 6-lead EEG also missed an ictal discharge emanating from the frontal lobe.

Conclusions: A limited 6-lead EEG is able to detect some common abnormal rhythms seen in AS but is sub-optimal in detecting overall background appearance and seizures in AS. In contrast to a general epilepsy population, IEDs are less likely to be detected on a prolonged EEG in AS patients, even when sleep is captured. Thus, an EMU admission may needed to characterize and localize seizures in this special population.

2.060

CLINICAL SIGNIFICANCE OF VERY HIGH FREQUENCY OSCILLATIONS (OVER 1000 HZ) IN EPILEPSY

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Rationale: We reported very high frequency activities of 1000-2500 Hz in highly localized cortical areas of patients with neocortical epilepsy recorded by subdural electrodes, and named these activities “very high frequency oscillations (VHFO)” (Usui et al., Clin Neurophysiol. in press). In this study, the clinical significance of VHFO was investigated.

Methods: Ten patients with intractable focal epilepsy (eight with neocortical epilepsy, and two with medial temporal lobe epilepsy) were studied. All patients underwent intracranial EEG monitoring. EEG recording with a sampling rate of 10 kHz was conducted. The presence or absence of VHFO, the location of VHFO, postoperative seizure outcome, and pathology were analyzed.

Results: In five patients with neocortical epilepsy and one with medial temporal lobe epilepsy, VHFO of 1000-2500 Hz was detected in highly localized areas. In all six patients with VHFO, the areas with VHFO were included in the seizure onset zone and irritative zone. In four of five neocortical epilepsy patients, surgical resection included the areas with VHFO. Three of these four patients have been seizure-free, and the remaining patient had simple partial seizures. In the fifth patient with VHFO, the area with VHFO was located over primary somatosensory area and was not included in the resection. She has also been seizure-free. Surgical resection was not performed in the medial temporal lobe epilepsy patient with VHFO. VHFO was not detected in the remaining three patients with neocortical epilepsy and one with medial temporal lobe epilepsy. In three neocortical epilepsy patients without VHFO, postoperative seizure outcome was favorable in one and unfavorable in the remaining two. One medial temporal lobe epilepsy patient without VHFO had an unfavorable outcome. Histology revealed cortical dysplasia in all five patients with VHFO. In three neocortical epilepsy patients without VHFO, cortical dysplasia was detected in two. Hippocampal sclerosis was detected in one patient with medial temporal lobe epilepsy.

Conclusions: The presence of VHFO may be related to favorable seizure outcome. Further studies are necessary to clarify the clinical significance of VHFO.

2.061

CHANGING SEMIOLOGY AND ITS RELATION TO FUNCTIONAL BRAIN NETWORKS IN CHILDREN WITH REFRACTORY PARTIAL EPILEPSY

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Rationale: Little is known on occurrence and causes of changing seizure semiology in the individual patient. We aimed to assess the relation between changing semiology and age in patients with partial epilepsy, and to elucidate the underlying functional brain networks.

Methods: Patients with refractory symptomatic or cryptogenic partial epilepsy were selected from the Dutch Collaborative Epilepsy Surgery Program, and included in this study if at least two consecutive ictal video EEG recording had been performed. We analyzed changes in semiology in relation to ictal onset zones in the individual patient. Cerebral MRI scans were available for each patient. Graph theoretical analysis will be applied to further elucidate the observed changes in ictal onset zones and semiology.

Results: Seizure semiology with age had changed in 14 of the 15 patients observed during consecutive video EEG recordings. Changes included appearance or disappearance of lateralization of motor function, automatisms, lowered consciousness, and postictal signs.

In 9 of the 15 children, changing semiology had been related to changing ictal onset zones. Progression in structural MRI abnormalities were identified in two children, potentially accountable for the change in both semiology and ictal onset zones. Graph theoretical analysis will be applied in the children with stationary lesions. In 5 out of 15 children, ictal onset zones had not changed. In one child, video EEG recordings were insufficient for analysis.

Conclusions: Semiology often changes with age in relation to changes in ictal onset zones. Structural alterations are accountable for this change only in the minority of patients. Graph theoretical analysis is applied as a novel model to relate changes in semiology to age. We suggest that new insights into the neural substrates for changing semiology/ epileptogenic zones we be gained.

2.062

CIRDA - CENTRAL INTERMITTENT RHYTHMIC DELTA ACTIVITY - A LOCALIZING INTERICTAL ABNORMALITY IN SURGICAL PARTIAL EPILEPSY

Lindsy N. Williams and J. Britton (Mayo Clinic, Rochester, MN)

Rationale: Intermittent rhythmic delta activity on electroencephalography has been described from the frontal lobe (FIRDA), temporal lobe (TIRDA) and occipital lobe (OIRDA), each with different clinical implications (Watemberg et al., 2007). Central intermittent rhythmic delta activity (CIRDA) has not been specifically described in the literature. We performed a retrospective study to identify all patients undergoing EEG at Mayo Clinic from 1998 to 2009 reported as showing CIRDA.

Methods: The electronic EEG report system at Mayo Clinic was queried to identify all EEG reports from 1998-2009 containing phrases indicating the presence of central intermittent rhythmic delta activity. Two cases were identified.

Results: Case 1: A 30 year old right handed man presented for evaluation of a 25 year history of medically intractable partial seizures. The seizures were manifested by numbness starting at the right side of the neck and moving down the right upper extremity with associated jerking, sometimes propagating to the lower extremity. The seizures happened on a near nightly basis as he was falling asleep. CIRDA was frequently noted in the left centrotemporal derivations on interictal EEG (Figure 1). Continuous video-EEG monitoring (CV-EEG) captured 11 typical seizures, showing ictal EEG onset in the left centrotemporal region. MRI showed focal cortical thickening with non-enhancing T2 hyperintensity involving left parietal region consistent with focal cortical dysplasia. SISCOM showed a concordant hyperperfusion abnormality in the region of the dysplasia.

Case 2: A 19 year old right handed man presented for medically intractable partial seizures since age 10. Seizures were manifested by a “numb” sensation then posturing and clonus of the right upper extremity. He often experienced post-ictal numbness and weakness of the right upper extremity lasting several minutes. These occurred multiple times a day. Left CIRDA was frequently seen on the interictal EEG (Figure 2). Fourteen typical seizures were recorded during CV-EEG. Ictal EEG showed rhythmic delta activity involving C3 and P3 at ictal onset during two seizures, but was indeterminate in 12. MRI and SISCOM were non-localizing. He ultimately underwent intracranial monitoring, stimulation mapping and an awake cortical resection which resulted in significant improvement in his seizures but a mild right upper extremity paresis.

Conclusions: CIRDA was identified in two patients with intractable peri-Rolandic epilepsy. In one case, CIRDA was the most localizing abnormality in the pre-surgical work-up. In the other, the abnormality was concordant with other seizure-localizing data. CIRDA is a previously unnamed abnormality, which can be of localizing significance in patients with intractable peri-Rolandic epilepsy.

1. Watemberg N, Linder I, Dabby R, Blumkin K, Lerman-Sagie T. Epilepsia 2007; 48 (2) 330-4.

IMAGE: images/906255_A.jpg

FIGURE 1: Case 1 Interictal EEG

IMAGE: images/906255_B.jpg

FIGURE 2: Case 2 interictal EEG

2.063

CAN WE EVOKE EPILEPTIC HIGH FREQUENCY OSCILLATIONS BY SINGLE PULSE STIMULATION? YES, WE CAN!

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Rationale: In focal epilepsy, spontaneous high frequency oscillations (HFOs: 80-500 Hz) occur in intracranial EEG recordings. HFOs seem a marker of epileptogenicity and can be useful to delineate the epileptogenic region. If they could be evaluated per-operatively, this

could improve epilepsy surgery. However, the clinical use is now compromised because artefact-free recordings in sleep, followed by time-consuming analyses, are needed. HFOs occur in brain regions that are sensitive to produce after discharges at electrical stimulation for function localization. With single pulse stimulation it has been demonstrated that spike-like delayed responses can be evoked, which are partly pathological. If pathological HFOs could be evoked likewise, this might improve the feasibility of using them for clinical purposes. We studied whether it is possible to evoke HFOs by single pulse stimulation.

Methods: A 32 year old female patient with longstanding temporal lobe epilepsy was evaluated for surgery with subdural electrocorticography. 64 channels were recorded at 2048 Hz sample rate and evaluated by stimulating each consecutive electrode pair with ten single pulses of one millisecond duration, with inter-pulse intervals of five seconds. The bipolar channels were visually evaluated for evoked HFOs after the EEG was high-pass filtered by comparing one second before the stimulus to one second after the stimulus. Responses were divided into early and delayed responses and into ripples (80-250 Hz) and fast ripples (250-500 Hz). Two channels were compared specifically: a seizure onset zone channel and a non-seizure onset zone channel.

Results: Early and delayed HFO responses could be evoked, both ripples and fast ripples. Ripple, fast ripple and spike responses all occurred significantly more often in the presumed seizure onset zone channel than in the non-seizure onset zone channel (paired t-test). However, spike responses also occurred in the presumed non-seizure onset zone channel, while HFOs did not.

Conclusions: HFOs can be evoked by single pulse electrical stimulation and might be more specific for the seizure onset zone than single pulse evoked spike responses. Single pulse may offer an easy method to evoke and evaluate pathological HFOs in clinical practice.

IMAGE: images/905651_A.jpg

2.064

ANTICONVULSANT TERMINATION OF SEIZURES IN NEONATES UNDERGOING WHOLE BODY HYPOTHERMIA FOR MODERATE TO SEVERE ENCEPHALOPATHY

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Rationale: Historically there is a poor response of neonatal seizures to typical anticonvulsants. We assess the ability of first line anticonvulsants to terminate seizures in infants undergoing whole body hypothermia.

Methods: Hypothermia: Therapeutic whole-body hypothermia was performed in 56 infants e" 36 wks gestation transported to our hospital within 6 hrs of life with either severe acidosis or perinatal complications at birth, and who had moderate or severe encephalopathy [Shankaran et al 2005]. Infants were cooled to an esophageal temperature of 33.5°C for 72 hours, then rewarmed at 0.5°C/hr to 36.5°C. Continuous video-EEG monitoring was initiated within 24hrs of life and continued throughout cooling and rewarming.

EEG Analysis: 53 patients had EEGs available for review for seizures. Medical records were reviewed for presence of clinical seizures and administration of anticonvulsants.

Results: 15 infants had eeg confirmed seizures. 11/15 (73%) had at least 1 clinical seizure. 4 (26%) had no clinical seizures. 7 (46%) patients had seizures terminated by phenobarbital alone. 6 (40%) required phenobarbital and fosphenytoin for seizure termination. 1 (6%) continued to have seizures despite phenobarbital, fosphenytoin, and levetiracetam administration.

Conclusions: Most seizures are controlled with either phenobarbital or phenobarbital and fosphenytoin, in contrast to literature on this population prior to hypothermia. Further work needs to be done to determine the relative contributions of hypothermia and continuous video eeg monitoring to improved seizure control in this population.

2.065

CLINICAL OUTCOME OF EEG FINDINGS AT 3-12 MONTHS OF AGE

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Rationale: To determine how specific abnormal EEG findings found between 3 and 12 months correlate with clinical outcome on long term follow up

Methods: This is a retrospective study of 358 infants who had at least one EEG in the first year of life and subsequent clinical assessment between ages 4 to 16 years. Clinical outcome parameters included epilepsy and neurologic outcome (intelligence, school performance, developmental milestones and neurological examination). Long term prognosis was classified into "Normal" when patients had normal clinical outcome parameters, "Minor Sequelae" when patients had mild abnormalities in clinical outcome parameters, "Major Sequelae" when patients had moderate to severe abnormalities in clinical outcome parameters, and "Epilepsy" when patients had seizures and were on medication

Results: 66 had normal outcome, 39 had minor and 253 had major sequelae. 234 had epilepsy on follow up and 106 had not. 117/358 had major abnormal EEG background of which 90% had major sequelae and 75% had epilepsy. 98/358 had abnormal sleep potentials of which 91% had major sequelae and 80% had epilepsy. 175/358 had epileptiform discharges of which 85% had major sequelae and 80% had epilepsy. 60/358 had ictal epileptiform discharges of which 93% had major sequelae and 86.5% had epilepsy. 53/358 had hypsarrhythmia of which (90%) had major sequelae and 76.5% had epilepsy. 192/358 had moderate to severe abnormal overall EEG impression of which 85% had major sequelae and 79% had epilepsy

Conclusions: Interictal epileptiform discharges, ictal epileptiform discharges and hypsarrhythmia in the first year were associated with major neurologic sequelae and with epilepsy. Abnormal EEG background and sleep potentials were associated with major neurologic sequelae but not definitely with epilepsy. 80 to 85% of children with a moderately to severely abnormal overall EEG impression in the first year were associated with major neurologic sequelae and/or epilepsy

2.066

THE SIGNAL DETECTING ABILITY OF THE SCALP DENSE ARRAY ELECTROENCEPHALOGRAM -SPIKE COMPARISON WITH THE SIMULTANEOUS SUBDURAL ELECTRODES-

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Rationale: It is said that the dense array electroencephalogram (dEEG) has better spatial resolution than the conventional. The purpose of this study is to evaluate the spike detecting ability of the dense array electroencephalogram.

Methods: A 21 years old right handed female with right neocortical temporal lobe epilepsy underwent subdural electrodes (SD) insertion, the inter-contacts distances were 1cm, followed by the focus resection over the anterior part of the right superior, middle and inferior temporal lobe. This patient has been seizure free after the surgery. During the subdural electrodes monitoring (SDM) we simultaneously monitored dEEG.

We compared the thirty SDM spikes and the same spikes on the dEEG.

Results: 83% of the SDM spikes were detected by the dEEG. The SDM spikes were divided into less than 2 contacts, 3 contacts, 4 contacts, 5 contacts, 6contacts, 7contacts, 8contacts, 9 contacts and more than 10 contacts.

55% of the less than 2 contacts of SDM were detected by dEEG. Most of them were from mesial temporal spikes. If more than 3 contacts were involved, the dEEG could detect the spikes with 100%.

Conclusions: The dEEG could detect most of the spikes with the order of 2cm. The spike detection rate of 83% is high. However the spikes from mesial structure could not be detected by the dEEG.

2.067

THE EFFECT OF YLANG-YLANG AROMA ON AUDITORY P300 EVENT-RELATED POTENTIALS IN TEMPORAL LOBE EPILEPSY

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Rationale: It has been repeatedly shown that attentiveness and alertness is impaired in temporal lobe epilepsy (TLE). Recently it has been reported that ylang-ylang aroma has positive effects on attentiveness and alertness. We investigated the effect of ylang-ylang essential oils on cognitive functions of patients with TLE by measuring P300 as event-related potentials.

Methods: The current study included thirteen TLE patients (34.1±10.6 years old, four females, twelve right-handed and one left-handed) and fourteen age-matched healthy controls. Six of thirteen patients were seizure free for more than twenty-two months. The laterality of epilepsy focus was left in four, right in one, bilateral in one, and unclear in the rest. The electroencephalogram was recorded from scalp electrodes including Fz, Cz, Pz, Oz and bilateral mastoids as participants inhaled air with ylang-ylang essential oils and an odorless control air. The stimulus series was composed of 1000Hz of frequent tones (80%) and 1050Hz of rare tones (20%). Rare tones were presented randomly with a 0.2 probability. At least 20 responses from rare stimuli were analyzed. Participants were instructed to watch a video screen showing of a cartoon story during sessions and to count the number of rare tones through earphones. P300 was evaluated as an averaged evoked potential waveform for the rare tones at Fz, Cz, Pz. The peak amplitudes and peak latencies between 300ms and 500ms were compared using analysis of variance (ANOVA) and t-test.

Results: P300 amplitudes were significantly reduced ($p<0.05$) by inhalation of the ylang-ylang aroma while latencies of P300 were similar between two conditions in healthy control group. In contrast, there were no significant differences in P300 amplitudes or latencies between two conditions in the TLE patients. In the patients group, there were no differences between the effect of ylang-ylang aroma on remission group and intractable group. Error rates in counting rare sounds on the aroma condition and the odorless condition for TLE group were almost the same as healthy controls.

Conclusions: Our results suggest that the effect of ylang-ylang aroma on the cognitive function reflected by the auditory P300 event-related potentials of patients with temporal lobe epilepsy may be limited, which might be related to impaired cognitive functions including attentiveness and alertness in TLE.

2.068

NONPHARMACOLOGICAL MANAGEMENT OF EPILEPSY COMORBIDITIES

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Rationale: Neurofeedback (NF) - facilitated regulation of the arousal state has been used effectively in the treatment of closed head injury1, insomnia2, migraine, depression3, ADHD4, and posttraumatic stress disorder5. A recent meta-analysis review concluded epilepsy was positively impacted by neurofeedback ($p = 0.001$).6 We therefore hypothesized that NF could serve as a therapeutic modality for epilepsy patients with refractory comorbidities. In the present study we applied a NF protocol to two male patients with well controlled seizures but with medically refractory comorbidities: insomnia, intractable headaches and ADHD in Patient A; episodic dyscontrol (self-banging/ mutilating episodes) in Patient B.

Methods: We obtained consent for NF therapy promoting central nervous system (CNS) self-regulation. Procedures were performed under physician direction and supervision (one of the authors). Patient A's implanted vagus nerve stimulator (VNS) device was temporarily inactivated for all his NF sessions. Initial NF trials sought an optimal reinforcement frequency (ORF) for each patient reflecting his optimal arousal state, based on subjective reporting by the patient as well as observer ratings of behavioral alertness. The ORF was established using bipolar training at T3-T4 (the ORF being within the clinical EEG band, particularly the infra-low region < = 0.1 - 1.5 Hz).7, 8 The T3-T4 bipolar recording was used to maximize the reward-based frequency feedback signal without promoting hemispheric coherence (of concern in individuals with seizures). Subsequently, each patient was scheduled to receive 21 separate 30-minute NF sessions (Othmer protocol9) over

a period of four weeks. Baseline performance tests (symptom profiles, TOVA10, QEEGs, and observer evaluations) were to be repeated after 21 sessions to compare results to pre-treatment baseline.

Results: (Table 1.) Patient A completed only 13 sessions (discontinuing for financial reasons). Nevertheless Patient A's medications for insomnia, headache, and ADHD were progressively discontinued and he remained seizure free on his original three antiepileptic drugs (oxcarbazepine, rufinamide, and zonisamide). Patient B's symptom profile was reduced 62.7% following 21 NF sessions; his seizures remained well-controlled on monotherapy (topiramate).

Conclusions: Early results support the hypothesis that NF is a useful therapeutic modality for managing epilepsy comorbidities without compromising seizure control. Furthermore, NF treatment can allow medications other than AEDs to be discontinued thereby averting potential adverse effects arising from multiple drug interactions. The therapy is not widely covered by insurance, limiting its heuristic evaluation. Intrinsic cortical hyperexcitability underlying common epilepsy disorders reflects disturbed mechanisms of CNS control and regulation. Because many epilepsy comorbidites are syndromic expressions of the same CNS dysregulation that gives rise to seizures, physician-driven protocols investigating the mechanisms by which NF works to control comorbidities may shed light on mechanisms of epileptogenesis.

IMAGE: images/895914_A.jpg

Patient Baseline Assessment and Response to Neurofeedback Therapy

IMAGE: images/895914_B.jpg

REFERENCES

2.069

EEG PRESENTATION IN RAPIDLY EVOLVING SPORADIC CREUTZFELDT-JAKOB DISEASE (SCJD)

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Rationale: EEG can be very useful in diagnosing prion infections and has been included in the WHO diagnostic criteria for sCJD. In practice, its value can be optimized when sequential studies are performed. The presence of EEG changes, including periodic sharp wave complexes (PSWC), may vary even at advanced stage. Monitoring the evolution of these findings may alert one to the correct diagnosis as other non-invasive diagnostic modalities are limited.

Methods: Observation of a patient with pathologically confirmed rapidly progressive sCJD (MM1) from the clinical onset to death, including EEG studies across 24 day period.

Results: An elderly right handed female presented with dizziness, gait disturbance and forgetfulness for 3 weeks. The initial neurological examination was significant only for mildly ataxic gait. In the following 3 weeks, she deteriorated rapidly with progressive worsening of ataxia, startle myoclonus, and cognitive decline leading to akinetic mutism. She died within 10 weeks after clinical onset of her disease. Brain MRIs showed persistent diffuse gyriform hyperintensity in the right more than the left hemisphere on diffusion weighted images. Neuron specific enolase was elevated in the cerebrospinal fluid. Right frontal brain biopsy and pathological studies showed vacuolization in cerebral gray matter, presence of protease resistant prion protein (PrPsc or PrP27-30), and immunopositivity to 3F4 monoclonal antibody. Three weeks after clinical onset, the first EEG showed asymmetric attenuation of background fast activities in the right hemisphere and generalized intermittent rhythmic slowing. The asymmetry became less evident during sleep. EEG monitoring was started 18 days later and lasted for 5 days. Compared to the initial record, progressive diffuse background slowing and intermittent suppression was noted. The amount of generalized intermittent rhythmic slowing remained stable and the asymmetric attenuation in the right hemisphere persisted throughout the entire period of observation. Abundant anteriorly dominant PSWCs were observed as intermittent bursts. Their temporal and spatial features, including an initial anterior positive deflection and a striking dominance in the right hemisphere, persisted throughout the monitoring. PSWCs attenuated briefly in response to intravenous lorazepam, though no clinical change was noted. No definite electrographic seizure were identified. The patient expired at home 4 weeks after the last EEG.

Conclusions: The value of EEG in diagnosing prion diseases can be improved by repeated recordings. Close monitoring of serial EEG changes and correlation with clinical symptoms may guide one to the correct diagnosis early.

As in our case, PSWC, which can be asymmetric, may persist into advanced stage of sCJD and should not be confused with periodic lateralized epileptiform discharges from other causes. In some cases as in our patient, serial EEG may provide evidence of prion disease and support further definitive invasive evaluation such as a brain biopsy.

2.070

METHODS OF SLEEP DEPRIVATION IN CHILDREN UNDERGOING SLEEP-DEPRIVED EEG

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Rationale: Sleep-deprived EEGs (SDEEG) are commonly used in clinical practice to detect sleep-induced epileptiform abnormalities, which are diagnostic indicators of specific types of epilepsy. While this is a very useful diagnostic technique, studies have shown that the SDEEG places a notable burden on both parents and children. One study reported that nearly fifty percent of parents found it difficult to keep their child awake at night and thirty percent of parents found it difficult to wake their child in the morning (1). Objective: To prospectively study the specific strategies used by parents and/or children to ensure sleep deprivation before undergoing a SDEEG. The findings of this study will be used to provide guidance for parents and children on how to adopt a convenient method of sleep deprivation.

Methods: Inclusion Criteria: 1) Children between 1-17 years who either had seizures or were suspected to have seizures. 2) Male and female participants were included, with no restrictions based on race or ethnic origin. Children referred from the neurology and general pediatrics outpatient clinics at McMaster Children's Hospital for a SDEEG during May 2008—ongoing, fulfilling the inclusion criteria, were studied. All participants were interviewed by either an EEG technologist or co-investigator and were administered a qualitative questionnaire. The questionnaire collected data about the patient's demographic details, previous EEG history, and sleep-deprivation strategies. The data collected was analyzed for trends and main themes.

Results: 93 patients (aged 16mos-17 yrs; mean 8.32 yrs) were interviewed (Table 1), to date. 82.8% of children had a previous EEG,

with 24.7% of all patients having had a previous SDEEG. Main themes identified for the patients were: 1) Instruction on amount of sleep deprivation; 52.7% of the patients were instructed on how many hours their child should sleep; 2) Parents' reactions to SDEEG; "Will my child fall asleep during EEG?" was the most common reaction (59.1%) and "I do not want to keep myself awake" was the least common (14.0%); 3) Strategies used to keep child awake at night; most common strategy (77.4%) was to watch TV; 4) Strategies used to keep child awake on trip to the hospital on the day of SDEEG; most common strategy (68.8%) was to constantly talk to child in the vehicle; 5) Success of strategies; 90.3% of children did not fall asleep on the trip to the hospital.

Conclusions: Certain sleep-deprivation strategies appear to be used across all seasonal and age-specific subgroups (watching TV, playing computer/video games, constantly talking). Indoor activities are largely preferred over outdoor activities, across all seasons. Outdoor activities for sleep-deprivation are most preferred during the summer months. Similarly, parents, across all patient age groups, are primarily concerned with whether their child will fall asleep during the SDEEG. The data collected can be used to help parents and children better cope with sleep-deprivation before SDEEG and to lessen their anxiety regarding adequate sleep deprivation.

Table 1: Methods of sleep deprivation

IMAGE: tables/908038_T1.jpg

2.071

SCOTOSENSITIVE MYOCLONIC EPILEPSY

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Rationale: Scotosensitivity is characterized by emergence of occipital spike and slow waves upon eye closure, or darkness and abates in response to eye opening in light room as well as fixation in dark. It has been classically described in early and late onset occipital lobe epilepsies. The scotosenstive occipital spikes are also reported to precede scotosensitve myoclonus occurring in the context of mitochondrial disease. The myoclonus is thought to represent the spread of this epileptiform activity from the occipital cortex to areas involving generation of motor movements. Here we present a case of scotosensitive ictal myoclonus with no occipital spikes in the EEG.

Methods: 22-year old right-handed male with no known cognitive deficits had his first generalized tonic clonic seizure at 17 years of age. His epilepsy became refractory to medication in the following 3-5 year and during periods of seizure exacerbation he had apparent cognitive decline. Family history was negative for epilepsy, myoclonus or neurodegeneration. Brain MRI showed no structural abnormalities and normal anatomy. Somatosensory evoked potentials were not enhanced. Genetic testing was deferred due to economical reasons. Video EEG monitoring was done with XLTEK video-electroencephalograph system and application of standard 10-20 electrodes.

Results: Clinically during the video EEG he had spontaneous myoclonus involving different cranial, axial and appendicular muscle at different times during wakefulness. Upon discontinuation of antiepileptic medication he was noted to develop eyelid, neck and appendicular myoclonia (including gluteal muscles). There was an increase in frequency of his myoclonic jerks as well as further alteration of consciousness prior to generalization. After resumption of antiepileptic medication he started to have axial myoclonus affecting abdominal and diaphragmatic muscles, causing hiccups for several days. Scotosensitivity was clinically demonstrated: upon eye closure or switching off the lights he had eye globe myoclonus, followed by neck and axial myoclonus affecting upper torso and shoulders. His EEG only showed high amplitude 2-4 Hz semirhythmic delta slowing during scotosensitive and spontaneous myoclonia. At no times he had spike bursts or sharp waves during or preceding his myoclonic events. There were no occipital spikes in response to darkness or photic stimulation.

Conclusions: There is no neurophysiological evidence of local cortical epileptic hyperexcitability preceding our patient's spontaneous or reflex myoclonus (i.e. there are no occipital spikes, pre-myoclonic spike bursts, interictal epileptiform discharges or enhanced evoked potentials). The myoclonus is precipitated by darkness pointing to involvement of widespread cortico-cortical (possibly occipito-frontal) connections as well as an imbalance of inhibitory and excitatory mechanisms. The subsequent development of a generalized seizure points to eventual epileptic network perturbations. Therefore we conclude that a disinhibitory network phenomenon may be the basis of our patient's motor myoclonus well prior to epileptic affection of cortical reflex loop.

2.072

PROSPECTIVE MULTICENTER STUDY ASSESSING THE CLINICAL ADDED VALUE OF MEG IN THE PRESURGICAL EVALUATION OF REFRACTORY PARTIAL EPILEPSY

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Rationale: MEG is increasingly used in presurgical evaluation of patients with refractory partial epilepsy (RPE) although its clinical value compared to other localization techniques is still under debate. This multicenter prospective blinded study assessed the clinical added value of MEG in presurgical evaluation of patients with RPE.

Methods: Between September 2007 and April 2010, 70 consecutive patients (42 males, mean age: 31,5 years, age range: 3-63 years) were prospectively included. Fourty-seven patients were followed at ULB-Hôpital Erasme (Brussels) and 23 patients at Ghent University Hospital. All patients had RPE and were not formally excluded from surgery after conventional non-invasive presurgical evaluation (CNIPE).

All patients underwent whole-head MEG recording (Elekta Neuromag, Elekta Oy) during one hour (eyes-closed rest, lying position). MEG data were visually inspected for interictal epileptiform discharges (IED). Corresponding equivalent current dipoles (g/%>80%) were fitted in patients' spherical head model and coregistered on their MRI.

Results of CNIPE were first discussed blinded to MEG results in respective multidisciplinary epilepsy surgery meetings to determine the presumed localization of the epileptogenic zone and the therapeutic attitude (A: focal resective surgery, B: invasive EEG monitoring (iEEGm), C: rejected except if new decisive information from MEG).

MEG results were then multidisciplinary discussed. The way MEG influenced the therapeutic attitude was assessed.

Results: Based on CNIPE, twenty-five patients had extra-temporal lobe epilepsy, 36 had temporal lobe epilepsy and 9 had unclear localization. The therapeutic attitude was A in 24 patients, B in 32 patients and C in 14 patients. MEG was unreadable in 3 patients, normal in 14 patients and showed IED in 53 patients (76%). MEG results did not change the therapeutic attitude in 56 patients (80%) but confirmed it in 97% of the cases when abnormal. MEG changed the therapeutic attitude in 14 patients (20%). MEG-related changes consisted in a reorientation from C to B in 3 patients and from C to A in 1 patient, in modifications of iEEGm electrode implantation plan in 5 patients and in additional neuroimaging investigations in 5 patients. MEG-related changes involved 36% of patients with extra-temporal lobe epilepsy, 44% of patients with unclear localization and 3% of patients with temporal lobe epilepsy.

Conclusions: Novel information brought by MEG changed the therapeutic attitude in 20% of patients with RPE who are potential candidates for surgery. MEG-related changes mainly involved patients with extra-temporal lobe epilepsy and unclear localization. MEG confirmed the management option in 97% of patients with no MEG-related change and abnormal MEG. We conclude that MEG is a clinically relevant non-invasive localization technique for presurgical evaluation of patients with RPE.

2.073

WHICH SPIKES ARE VISIBLE ON MEG? - THREE CASE REPORTS OF SIMULTANEOUS RECORDINGS OF INTERICTAL EPILEPTIFORM DISCHARGES BY MEG AND INVASIVE STEREO-EEG

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Rationale: MEG has an inherently higher spatial resolution and may detect epileptiform discharges, which cannot be detected by scalp EEG. MEG is being increasingly used as a part of the non-invasive presurgical evaluation of patients with pharmacoresistant epilepsy. However, as is the case with scalp EEG, not all epileptiform discharges can be detected by MEG, and it is not clear which spikes are visible on MEG.

Methods: We included three patients with pharmacoresistant epilepsy, who had stereotyped repetitive interictal spiking on intracranial stereo-EEG recordings.

Patient 1 (18 year old, male): Seizures started at 15 months of age, and were characterized by right arm and leg tingling followed by generalized convulsion. Video-EEG monitoring (VEEG) showed interictal spikes in the bilateral paracentral regions and EEG seizures arising from the vertex region. MRI was normal and ictal SPECT suggested a left posterior insular onset.

Patient 2 (30 year old, male): Seizures started at age 19 years, and were characterized by "tunnel vision" or psychic aura followed by staring. VEEG showed no interictal epileptiform discharges, but one EEG seizure arising from the right temporo-parietal region. MRI demonstrated a small area of abnormal cortical thickness and signal involving a deep sulcal aspect of the posterior segment of the right superior temporal sulcus.

Patient 3 (30 year old, male): Seizures started at age 12 years, and were characterized by tingling sensation in the throat followed by drooling and garbled speech without loss of awareness. VEEG showed no interictal epileptiform discharges and non-localizable EEG seizures. MRI was normal. PET scan showed subtle hypometabolism in the right fronto-temporal operculum and ictal SPECT suggested a right posterior insular onset.

MEG was recorded with a 204 planar gradiometer MEG system (Neuromag, Helsinki, Finland) with simultaneous stereo-EEG. To obtain stereo-EEG recordings intracranial depth electrodes were placed stereotactically following a comprehensive noninvasive evaluation and discussion in a multidisciplinary patient management conference. MEG source localization of interictal epileptiform discharges was obtained using standard equivalent current dipole (ECD) methods.

Results: Despite technically good MEG recordings, in two of the three patients repetitive spiking was only detected by the stereo-EEG electrode traversing the restricted irritative zone in the parietal operculum and the depth of the superior temporal sulcus, respectively. In the third patient, MEG detected discharges corresponding to the repetitive spiking seen on stereo-EEG involving a wider area in the frontal operculum. A single tight cluster of ECDs was estimated in the right parietal operculum and posterior insula by MEG.

Conclusions: MEG is a non-invasive technique capable of recording some "deep" spikes arising from a relatively large cortical region. Intracranial EEG (specifically stereo-EEG in these three patients) is more sensitive than MEG for the detection and localization of the epileptogenic cortex.

2.074

MAGNETOENCEPHALOGRAPHY USING TOTAL INTRAVENOUS ANESTHESIA IN PEDIATRIC PATIENTS WITH INTRACTABLE EPILEPSY: COMPARISON OF SPIKE SOURCES WITH AND WITHOUT PROPOFOL

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Rationale: Sedation for uncooperative pediatric patients is important to keep patients still during magnetoencephalography (MEG) measurement. We previously reported Total intravenous anesthesia (TIVA) of propofol affecting MEG spike sources (MEGSSs) especially for the patient without lesion. The purpose of this study is to evaluate the effect of propofol for MEG in same patients with and without TIVA.

Methods: From August, 2000 to March, 2008 we performed MEG on 651 pediatric patients with intractable epilepsy. Among them 79 patients (12%) underwent MEG with TIVA. There were 10 patients underwent MEG with and without TIVA at the different time. There were 3 boys and 7 girls (age 14 months to 9 years old, mean age with TIVA 3.6 years old, mean age without TIVA 4.7 years old). We maintained Propofol 30-60μg/kg/min with remifentanil using nasal prong, laryngeal mask airway or endotracheal tube. MEG was

performed with whole-head 151-channel gradiometers. Sampling rate was 625 Hz. We recorded 15 to 20 data sets of 2-minute periods.

Results: Propofol of TIVA reduced the MEG spikes/minutes (3.5 with vs 5.7 without TIVA) and the MEGSSs/minutes (0.8 with vs 2.6 without TIVA). Propofol TIVA minimized the size of clustered MEGSSs in 5 patients, slightly expanded MEGSS cluster in one patient. MEGSSs disappeared under TIVA in 4 patients. The reduced and minimized cluster of MEGSSs under TIVA remained in the epileptogenic zone in 5 of 7 patients who underwent surgery. Five of 6 patients (83%) with neuronal migration disorders (NMDs) remained MEGSSs under TIVA.

Conclusions: For the uncooperative patients with intractable localization related epilepsy, MEG with TIVA was worth performing for presurgical evaluation. Remaining lateralized MEGSSs with TIVA indicated the epileptogenic hemisphere to proceed resective surgery. The size of clustered MEGSSs can be minimized by TIVA. NMDs were intrinsically epileptogenic to present clustered MEGSSs even with TIVA.

2.075

IS A CORTICAL FOCUS DRIVING A CORTICO-THALAMIC CIRCUIT IN HUMAN ABSENCE EPILEPSY?

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Rationale: To describe the cortical cortico-thalamic circuit involvement during the evolvement of MEG spike-and-wave discharges (SWDs) in order to identify a focal cortical onset zone in human absence epilepsy using MEG.

Methods: MEG recordings were performed for 21 patients (6-15 years of age) with absence seizures, ranging from patients with childhood (CAE) or juvenile (JAE) absence epilepsy who can be treated quite successfully with anti-epileptics, to patients with more complex atypical forms of absence epilepsy and children who both had absences and complex partial clinical features. For each seizure of these children a non-linear association analysis was performed for time windows moving through the SWDs present in the MEG, similar to the analyses as used in the study of Meeren et al. (2002). Next, an average association strength was obtained based on all association values calculated for each possible combination of MEG sensors. This function was used for monitoring the time varying spatial distributions of the SWDs.

Results: Studying in detail the changes in time and space of the association strength revealed three distinct phases of the SWDs. The generalized 3 Hz SWDs showed, like in the study of Westmijse et al. (2009), a recurrent pattern of focal regional activity during the spikes alternated by generalized activity during the slow-wave phase of the SWDs, indicating most likely the involvement of a cortico-thalamic network. The focal regions that are present during the spikes of the SWDs, also appear to be present during the period from the first spike visible in the MEG to the first generalization and indicate the involvement of the bilateral frontal and parietal regions. Furthermore, the association analysis enabled the identification of a driving node of the SWDs in the period before generalization or even before the first visible spike in the MEG for 18 out of the 21 patients studied. These results will be discussed in relation with the source analysis results of the driving node activity, using either dipole analysis or beamforming source analysis in the time- and frequency domain.

Conclusions: Spatiotemporal association analysis is helpful in identifying the driving cortical node of the SWDs of patients with generalized absence epilepsy. The location of the driving node appears to differ for the clinically distinct patient populations, whereas the activity underlying the generalized SWDs seems to share a common network during the evolvement of these discharges for all patients studied.

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2.076

POSTOPERATIVE SEIZURE OUTCOMES WHEN INTERICTAL MEG CONCORDANT WITH ICTAL DEPTH EEG

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Rationale: Interictal magnetoencephalography (MEG) is often done as one of multiple tests to localize the likely epileptogenic zone in patients with medically intractable epilepsy undergoing evaluation for resective treatment. We compared interictal MEG results with intracerebral depth EEG ictal onsets in the context of postoperative seizure control.

Methods: The clinical courses of 45 consecutive patients with medically intractable epilepsy who underwent implantation of intracerebral depth electrodes at UCLA Medical Center between May 2000 and October 2005 were retrospectively reviewed. Of these 45 patients, 30 had interictal MEG. We evaluated the concordance of interictal MEG epileptiform dipoles with depth EEG ictal onsets. Concordance was classified as intralobar (group A), lobar (B), lateralized (C), bilateral homotopic (D1), bilateral homotopic interictal MEG with unilateral depth (D2), non-concordant unilateral MEG and bilateral depth (D3), non-concordant multifocal MEG and depth (D4), and contralateral non-concordant (E). The lack of depth lateralization or localization was classified as group (F) and the lack of MEG dipoles as (G).

Results: Twenty-two of the 30 presurgical candidates who underwent both MEG and depth EEG studies subsequently had resective surgery; and 20 resected patients had postoperative seizure outcome follow-up with durations ranging from 10 to 96 months (mean 50). Seizure outcomes corresponded to our MEG-depth EEG concordance classification as follows. The concordant groups (A, B, C, D1, D2) comprised 22 of the 30 total patients; 17 of these patients underwent resection, with postoperative seizure outcomes of: Engel class I (11 patients) & class IV (6). The non-concordant groups (D3, D4, E)

comprised 2 of the 30 total patients; one underwent resection, with Engel class IV outcome. The groups in which one of the two tests yielded no information (F, G) comprised 6 of the 30 total patients; 2 underwent resection, with seizure control outcomes of Engel class I for the one resected patient with no interictal MEG dipoles and Engel class II for the one resected patient with no lateralizing or localizing depth EEG ictal findings.

Conclusions: Clinical use of MEG is becoming increasingly routine and has been supported by clinical research results and professional guidelines. However, standardized use has not developed. In our results, the majority of our presurgical candidates had some degree of concordance of interictal MEG epileptiform dipoles and depth EEG ictal onsets. Our results suggest that the significance of concordance of interictal MEG with depth EEG in presurgical evaluation for resective epilepsy surgery is complex and requires further analysis. A larger case series may be needed to address this question.

2.077

MEG SOURCE LOCALIZATION OF EPILEPTOGENIC ZONE IN CHILDREN WITH PORENCEPHALIC CYST

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Rationale: Porencephalic cyst is a brain lesion caused by early ischemic insult or hemorrhage. We evaluated magnetoencephalography (MEG) spike source to localize the epileptogenic zone in children with intractable epilepsy secondary to porencephalic cyst.

Methods: We retrospectively studied 14 children with intractable epilepsy secondary to porencephalic cyst (6 girls; 8 boys; age range 2-19 years at MEG), who underwent prolonged scalp video-EEG, MRI and MEG. Interictal MEG spike source (MEGSS) locations were compared to ictal and interictal zone from scalp video-EEG.

Results: MRI showed porencephalic cysts in extratemporal lobes in 7 patients, within temporal lobe in 5, extending temporal region in 2. MEGSSs were clustered in the margin of the porencephalic cyst in all 14 patients. One single cluster of MEGSSs was seen in 13 patients, two clusters in 1 patient. Ictal EEG discharges were lateralized and concordant to MEGSS hemisphere in 9 patients (64%). Ictal EEG discharges were localized in one lobe in 1 patient, 2 lobes in 4, and diffuse hemisphere in 4. The other 5 patients showed generalized or diffusely undetermined ictal EEG discharges. Interictal EEG discharges were lateralized in 9 (64%) patients consisting of one lobe in 2 patients, two lobes in 2 patients, and diffuse hemisphere in 5 patients. Five patients had resective surgery. Two patients underwent lesionectomy plus MEGSS clusterectomy. One patient had resection after intracranial video EEG and one patient had first lesionectomy plus MEGSS clusterectomy and few years later, resection following intracranial video EEG. Temporal lobectomy and amygdalalohippocampectomy was performed in one patient. All of them achieved seizure freedom following surgery.

Conclusions: Scalp video EEG had a difficulty of lateralizing and localizing their interictal and ictal epileptiform discharges correlating with porencephalic cysts. MEG accurately delineated single or multiple marginal epileptogenicity surrounding porencephalic cysts in children with intractable epilepsy. Complete resection of MEGSSs clustered aside of porencephalic cysts can provide favorable seizure outcomes.

2.078

STAT MAGNETOENCEPHALOGRAPHY — AN EMERGENCY TOOL WHOSE TIME HAS COME

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Rationale: While magnetoencephalography (MEG) examinations are not infrequently ordered to be done on the same day, e.g. for pre-operative mapping of eloquent cortex prior to resective lesion surgery, these are still elective tests. Adequate sampling of the patient's spontaneous brain activity or multi-sensory evoked field protocols normally dictate a relatively lengthy survey. The sophisticated pre-recording setup required, vulnerability to artifact from acute care instrumentation, and perceived necessity for some degree of patient cooperation; followed by the tedious and lengthy post-processing and interpretation time, has precluded the use of MEG in truly emergent circumstances.

Yet the inherent properties of MEG actually make it well-suited for use in acute care situations. It has high te poral and spatial resolution, and once head positioning (HPI) coils have been attached to the scalp, the patient is ready.

Methods: The primary obstacles to rapid and safe MEG testing were evaluated and standard operating procedures developed including:

1) Technical feasibility. Issues related to indwelling lines, ventilators, etc. Presence of intensive care personnel, emergency medications, and access to immediate help.

2) Patient safety. Continuous monitoring, immediate entry into the MSR, guarding against most likely risks.

3) Speed of setup and recording. Maximal round-trip time from the ICU established at 1 hr.

4) Timely review, interpretation, and reporting. Focus on answering specific, immediate clinical question.

Arranging these solutions required the involvement of nursing, pharmacy, EEG technologists, engineering, as well as the medical staff/ fellows.

Results: During a one month period (3/16 - 4/14/2010) we performed 3 emergency MEGs which are illustrative of the indications and benefits for stat MEG testing.

Patient S was in a coma of unknown origin with frequent waves of widespread body tremor. EEG was unhelpful because the continuous artifact could not be distinguished from seizure activity. The patient was not on a ventilator, so paralytics could not be given to eliminate EMG artifact on EEG. The MEG was recorded in order to ascertain whether the patient's coma was due to seizures.

Patient H had had 2 right temporal lobectomies, and was in status epilepticus. The neurosurgically altered anatomy made it impossible to ascertain from EEG from where the focal status was arising. Because of its immunity to alterations in conductivity, the MEG was able to properly identify the origin of the epileptic activity.

Patient G underwent a repeat MEG, this time after placement of SEEG electrodes. These invasive electrodes appeared not to be sampling the epileptogenic region, but required immediate explantation. The MEG

was carried out just before removal to simultaneously view the SEEG and MEG signals, in order to plan a future invasive investigation.

Conclusions: Whole head magnetoencephalography can be safely and rapidly carried out in emergency circumstances. Targeted clinical neurophysiological questions permit truncated recording time and rapid feedback to the neuro-intensivist.

2.079

SENSITIVITY OF MEG TO INTERICTAL EVENTS ARISING FROM THE IRRITATIVE AND ICTAL ONSET ZONES: FINDINGS FROM SIMULTANEOUS MEG-IEEG RECORDINGS

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Rationale: To test the sensitivity of Magnetoencephalography (MEG) to interictal discharges arising from the irritative and the ictal onset zones (as described by intracranial EEG).

Methods: 6 consecutive epileptic patients were implanted with MEG-compatible subdural/deph electrodes in order to complete prolonged presurgical epilepsy monitoring. Ictal events were reviewed to define the extent of the ictal onset zone. Then, simultaneous intracranial EEG and MEG recordings were conducted for 30 minutes to characterize interictal events. Those interictal iEEG events sharing topography with the ictal onset zone (previously defined from prolonged video iEEG) were identified. The cortical area corresponding to each interictal iEEG discharge was calculated and the presence/absence of an associated MEG discharge was tested.

Results: Out of the 859 interictal iEEG discharges analyzed 311 (30%) produced an associated MEG spike. Interictal iEEG events arising from the ictal onset zone (137) produced a corresponding MEG discharge in 74% of the cases (102). MEG detected a 5% of the discharges with a source area under 8 cm2 and 70% of the discharges with a source area of 12 cm2 or higher; which included the vast majority of the interictal spikes generated from the ictal onset zone (87%).

Conclusions: Interictal MEG recordings are sensitive to interictal discharges arising from the ictal onset zone. Approximately 1/3 of the spikes detected during interictal MEG recordings arise from the ictal onset zone.

2.080

BILATERAL ASYMMETRIES IN THE MAXIMAL ACTIVATION OF SAME SUBJECT SSEP'S

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Rationale: Presurgical mapping using MEG in children with medically intractable seizures is fraught with difficulty. Children with epilepsy often have atypical motor and language activation patterns (1)(2). Given the gravity of the situation, identifying reliable and reproducible methods for determing neurophysiologic effects associated with epileptic foci are particularly vital. In this study, we evaluated using the temporal pattern of somatosensory response to predict epileptic hemispheric involvement.

Methods: Eighteen pediatric patients (18) with medically intractable epilepsy were examined at the Neuroscience Institute at Le Bonheur Children's Hospital (Memphis, TN). A whole head Magnes 3600 WH (248-channel) (4D Neuroimaging, Inc., San Diego, CA) was used to identify the somatosensory function areas. MEG data was analyzed using the equivalent current dipole method implemented in SPM8 (www.fil.ion.ucl.ac.uk/spm). Data was coregistered to the MNI305 3D T1 template for conformation of MSI localizations. Using Posterior Probability Maps (PPM) of source localized SSEP's, we identified the activated voxels in Brodman areas 2 and 3. We then plotted the time course of those voxels and selected the time of maximal activation.

Results: Three patients demonstrated unilateral activation and were excluded from the study. Fourteen of the remaining 15 patients demonstrated significant delay in the time of maximal activation compared to the contralateral side. In eleven of the fourteen, the delayed side was also the same hemisphere known to contain the epileptic foci. No significant difference was found in a Left vs. Right comparison. No correlation was found with age or handiness.

Conclusions: This preliminary study demonstrates the promising potential of using the temporal characteristics of the equivalent current dipole to determine hemispheric localization of epileptic foci. This method is important in that it might be used in cases when a resting state recording could not be acquired or is technically unsuccessful.

IMAGE: images/907963_A.jpg

Example of PPM of Left Brodman area 3 (Talairach -45,-18,44).

2.081

YIELD OF MAGNETOENCEPHALOGRAPHY IN MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Magnetoencephalography and Magnetic Source Imaging(MEG/MSI) is the most recent significant advance in the noninvasive localization of seizure foci. Mesial Temporal Lobe Epilepsy(MTLE) is the most common form of intractable epilepsy that requires epilepsy surgery as estimated by the NIH.It was the purpose of this study to determine the yield of MEG/MSI in mesial temporal lobe epilepsy.

Methods: This is a retrospective study of intractable mesial temporal lobe epilepsy patients who underwent MEG/MSI for seizure focus localization. The total number of intractable mesial temporal lobe epilepsy patients who underwent a MEG/MSI study was six. Mesial Temporal lobe epilepsy(MTLE) was defined as findings characteristic of MTLE in seizure description, Video-EEG, MRI Brain and PET. A whole head 306 channel MEG system was used with the sensor array equipped with 102 triple-sensor elements evenly distributed over the surface of the patient's head. The helmet array is configured with 306 independently sampled sensors. The recording was done in six 10 minute epochs for a total of 60 minutes.

Results: In 3 out 6 patients we identified MEG spikes in the ipsilateral temporal lobe. In these 3 patients the unilateral temporal dipoles, were localized to the same temporal lobe as determined by the other

diagnostic modalities - seizure description, Video-EEG monitoring, MRI Brain and PET. In the other 3 patients no MEG spikes were identified despite recording for a total of 60 minutes. So the yield of MEG/MSI in MTLE in our study was 50%. MEG systems with different configurations of magnetometers and gradiometers can potentially have different senstivity in detection of mesial temporal spikes.

Conclusions: Magnetoencephalography can detect mesial temporal spikes in about 50% of cases. In these cases it localizes the seizure focus accurately. Larger prospective studies will be needed to better establish the utility of MEG/MSI in MTLE.

2.082

CHARACTERIZATION OF MAGNETOENCEPHALOGRAPHIC INTERICTAL EPILEPTIFORM DISCHARGES WITH TIME-RESOLVED CORTICAL CURRENT MAPS USING THE HELMHOLTZ-HODGE DECOMPOSITION

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Rationale: Source estimates performed using a single equivalent current dipole (ECD) model for interictal epileptiform discharges (IEDs) which appear unifocal have proven highly accurate in neocortical epilepsies, falling within millimeters of that demonstrated by electrocorticography. Despite this success, the single ECD solution is limited, best describing sources which are temporally stable.

Adapted from the field of optics, optical flow analysis of distributed source models of MEG or EEG data has recently been proposed as a means to estimate the current motion field of cortical activity, or "cortical flow". This technique can be used to estimate local kinetic energy of cortical surface currents, and has been used to characterize correspondence between the speed and direction of the surface current flow within the visual cortex and the dynamical properties of the visual stimulus itself. The motion field so defined can be used to identify dynamic features of interest such as patterns of directional flow, current sources and sinks.

The Helmholtz-Hodge Decomposition (HHD) is a technique frequently applied in fluid dynamics to separate a flow pattern into three components: 1) a non-rotational scalar potential **U** describing sinks and sources, 2) a non-diverging scalar potential **A** accounting for vortices, and 3) an harmonic vector field **H**. As IEDs seem likely to represent periods of highly correlated directional flow of cortical currents, the **U** component of the HHD suggests itself to characterize spikes in terms of current sources and sinks.

Methods: Source Localization Cortical surface segmentation and tessellation from brain MRI was obtained using BrainSuite software (http://www.loni.ucla.edu/Software/BrainSuite/). The BrainStorm Toolbox (http://neuroimage.usc.edu/brainstorm/) was used for all subsequent source analyses. The computed head and cortex models were used in combination with the MEG fields to compute an estimate of current-source density distribution over the cortex based on a minimum norm estimate.

The ECD location, orientation and moment was calculated for each spike. For each spike identified, a time period covering spike onset, peak and offset was subjected to optical flow analysis, and subsequent HHD. The time of the maximum value of the global **U** component prior to peak occurrence was used to calculate the HHD source map.

Results: MEG data corresponding to 24 spike or sharp wave discharges from six patients with refractory epilepsy was subjected to the HHD analysis. Current sources and sinks with a location proximal to that of the calculated dipole were identified for approximately one third of the events. Figure 1 illustrates the ECD corresponding to the current source identified and and projected in figure 2 (along with the original spike).

Conclusions: For MEG detected spikes, the HHD offers an additional means of characterization of the spatial distribution of the discharge over time. For a subset of spike discharges, there appears to be a good anatomic correlation with the calculated spike dipole.

IMAGE: images/904983_A.jpg

IMAGE: images/904983_B.jpg

2.083

SYNTHETIC APERTURE MAGNETOMETRY-KURTOSIS (SAM(G2)) FOR SINGLE/MULTIPLE EPILEPTIC FOCI IN CHILDREN WITH NEOCORTICAL EPILEPSY

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Rationale: Magnetoencephalography (MEG) has been typically using modeling interictal activity as equivalent current dipoles (ECDs) to localize epileptic activity. Synthetic aperture magnetometry (SAM) is an adaptive spatial filtering algorithm for MEG. SAM kurtosis (SAM(g2)) provides source locations with excess kurtosis value (steepness) of spikes. To evaluate SAM(g2) in analyzing single/multiple epileptic foci, we applied SAM(g2) in children with intractable neocortical epilepsy.

Methods: We analyzed SAM(g2) and equivalent current dipoles (ECDs) in 44 children (mean 9.9 years). We used whole head gradiometer Omega system (151 channels). SAM(g2) calculated kurtosis value (band pass filter, 20-70 Hz) at each voxel (5 mm distance). We selected epileptic voxels of SAM(g2) (evSAM(g2)) with local peak kurtosis higher than half of maximum value and more than 1.0 (background activity). A cluster of ECDs contains e"6 ECDs and a group of evSAM(g2) contains e"3 evSAM(g2), within 1cm distance of each other. We evaluated the concordance of evSAM(g2) with both single and multiple clustered ECDs, with and without lesions. We defined a case as "concordant" when e" 50 % of grouped evSAM(g2) overlapping with ECD clusters; "partially concordant" when < 50 %; "discordant" when there was no overlap.

Results: The rate of grouped evSAM(g2) overlapping with ECD clusters ranged from 0 to 100 % with a mean of 73.1%. Thirty-four patients (77.3%) showed "concordant" with 20 single ECD clusters (11 lesions; 9 non-lesion) and 14 multiple ECD clusters (12 lesions, 2 non-lesion). Seven patients (15.9%) showed "partially concordant" with 2 single ECD clusters, (2 non-lesions) and 5 multiple ECD clusters (3 lesions, 2 non-lesions). Three patients (6.8%) showed "discordant". Eleven patients with single ECD cluster with lesion showed higher

concordant rate (mean 88%) than that of 12 patients with a single cluster without lesion (67.4%). Sixteen patients with multiple clusters with lesion also reached higher concordant rate (74.6%) than that of 5 patients without lesion (49.4%). In thirteen patients who underwent surgery, nine patients became seizure free and four had reduction in seizure frequency.

Conclusions: SAM(g2) analysis succeeded in localizing epileptic sources correlating with both single and multiple clustered ECDs in patients with neocortical epilepsy. SAM(g2) showed highest concordant evSAM(g2) with the single clustered ECDs secondary to lesion. In multiple clustered ECDs, lesional epilepsy presented highly concordant evSAM(g2) comparing with those without lesion. SAM(g2) can assist ECD especially for the cases with multiple foci to determine epileptogenic hemisphere and surgical candidates.

2.084

MAGNETOENCEPHALOGRAPHY OF SPIKE AND WAVE DISCHARGES IN DRUG NAIVE CHILDHOOD ABSENCE EPILEPSY

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Rationale: Childhood absence epilepsy (CAE) is characterized by seizures consisting of brief impairments of consciousness with bilaterally synchronous 3 Hz spike and wave discharges (SWD) on EEG. This study was undertaken to examine the feasibility of using magnetoencephalography (MEG) to measure SWDs in patients with newly diagnosed and untreated CAE. The corticothalamic system plays a major role in the underlying pathophysiology of CAE. The specific areas of thalamus and cortex that are crucial for the initiation, propagation, and termination of SWDs are still unclear. This is in part because it has been difficult to couple the temporal resolution of epileptic discharges with the spatial resolution needed to identify specific groups of neurons. The purpose of this study was to determine if the fast activity component of SWDs could be recorded within thalamic nuclei.

Methods: Children, aged 8 to 11 years old, with newly diagnosed and untreated CAE were recruited for the study. Protocols for MEG recording were similar to those used for conventional EEG. MEG recordings were completed in 10 minute time blocks for a total of 40 minutes, with hyperventilation used as provocation if needed. MEG signal analysis was completed using the beamformer technique for the time periods of several milliseconds before and after the appearance of SWDs. Data was analyzed at frequency bandwidths of 5 Hz to 70 Hz and 20 Hz to 70Hz. Virtual sensors were placed within the thalamus as well as in the frontal, parietal, temporal, and occipital cortices. MEG recordings were conducted on a 275 channel CTF magnetometer and MEG signal was analyzed with source localization software including the beamformer technique.

Results: Four children, aged 8 to 11 years old, with newly diagnosed and untreated CAE were recruited for the study. A total of ten absence seizures occurred during MEG recording. High frequency MEG activity was seen within the frontal, temporal, and occipital cortices as well as the thalamus during all seizures. Activity was diffuse and bilateral within the thalamus whereas cortical activity was more focal and bilateral. The thalamic bursting pattern did not mirror the activity within the cortex, suggesting that it may be an independent generator.

Conclusions: Using MEG, we have been able to detect focal areas of activity within the thalamus and cortex during absence seizures in patients with untreated CAE. Activity within the thalamus did not mirror that found within the frontal, temporal, and occipital cortices in either amplitude or timing, suggesting that thalamic activity is independent of that within the cortex. These data indicate that MEG may be a useful tool for studying generalized epileptiform discharges that involve both cortical and subcortical regions of the brain. The high temporal resolution and very good spatial resolution of MEG could provide more information regarding the initiation and propagation of generalized seizures than has been possible to date with other imaging modalities.

2.085

MEG FUNCTIONAL CONNECTIVITY AND COMPLEX NETWORKS RELATE TO CLINICAL CHARACTERISTICS OF LESIONAL EPILEPSY PATIENTS

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Rationale: Epilepsy is common in patients with circumscribed brain abnormalities, such as primary brain tumours and hippocampal sclerosis. The mechanism of seizure onset that is induced by these abnormalities remains poorly understood. It has been suggested that the interaction of the ictal zone with surrounding brain areas is pivotal in the initiation and particularly in the propagation of seizures. A way to explore the interactions between brain areas is to look at functional interactions or functional connectivity. Furthermore, the brain can be seen as a complex network of interacting brain regions. Modern network theory can be used to analyze the characteristics of this network.

We compare functional networks derived from MEG recordings in lesional epilepsy patients to those in healthy controls. Furthermore, we report on the relationship between functional connectivity and network characteristics on the one hand, and clinical characteristics on the other hand in lesional epilepsy patients.

Methods: Resting-state eyes-closed MEG-recordings of 35 lesional epilepsy patients and 36 healthy controls were analyzed. The phase lag index (PLI) was used to assess functional connectivity in conventional frequency bands and weighted networks were constructed. Group differences between patients and controls in PLI and network parameters were calculated, and the correlation between functional connectivity, network measures, and clinical characteristics was established.

Results: Clustering in the theta and lower alpha bands was increased in lesional epilepsy patients. Furthermore, longer theta band path lengths were correlated with higher seizure frequency, longer epilepsy history, and use of multiple anti-epileptic drugs. Finally, theta band clustering and path length differed between patient with different lesion pathology.

Conclusions: Interictal functional network topology in lesional epilepsy patients is altered compared to controls, in particular in the theta band. Furthermore, network topology is correlated with several clinical epilepsy characteristics.

Correlations of PLI theta band and network properties with clinical characterstics

IMAGE: tables/905215_T1.jpg

Table 3. Correlations of PLI theta band and normalized local clustering and path length with clinical characterstics. Correlations with epilepsy history and seizure frequency were calculated by means of Kendall's Tau correlation coefficients (Tau). Group differences based on AED monotherapy versus polytherapy, lesion type, and lesion lateralization were calculated by means of Mann-Whitney U-tests. An asterisk marks significance at the $p < 0.05$ level; a double asterisk marks significance at the $p < 0.01$ level. Correlations are only shown for $p < 0.1$.

Abbreviations: PLI=Phase lag index; Cw/Cws=normalized clustering coefficient; Lw/Lws=normalized path lenth; S=small-world index; LGG=low-grade glioma; HGG=high-grade glioma.

IMAGE: images/905215_A.jpg

Connection differences Theta band PLI connections that differ between patients and controls at the $p < 0.01$ level. Connections that are decreased in patients are shown in the left figure, connections with increased strength in patients are shown on the right. In general, connections in patients seem increased, especially in the central, occipital and parietal regions of the right hemisphere.

2.086

MEG AIDS INTERPRETATION OF EPILEPTIC ACTIVITY PROPAGATION WHERE INVASIVE ELECTRODE SAMPLING IS INADEQUATE

Zhong I. Wang, J. C. Mosher, R. C. Burgess, K. Jin, Y. Kakisaka, I. M. Najm and A. V. Alexopoulos (Epilepsy Center, Cleveland Clinic, Cleveland, OH)

Rationale: When epileptic activity is propagated, source localization analysis may be misleading. Studies have demonstrated that the propagation of seizures may share similar pathways to the course of interictal spikes. Understanding the patterns of propagation is essential and closely related to a favorable surgical outcome. In this study, we present a series of patients whose interictal spikes showed clear propagation patterns as revealed by Magnetoencephalography (MEG). Our aim was to take advantage of MEG's strengths to improve the interpretation of intracranial electroencephalography (ICEEG) recordings.

Methods: We selected patients with medically intractable epilepsy who underwent MEG and ICEEG studies between Oct. 2009 and May 2010. We selected those whose interictal spikes showed clear propagation patterns. MEG was recorded by a 306-channel system (Neuromag, Helsinki, Finland). Source localization analyses were performed with Curry 6.0 (Neuroscan, Hamburg, Germany), using standard single dipole analysis, and a minimum norm method with current density reconstruction constrained by the cortical surface generated with the individual's MRI. MEG source localization, involved channels on ICEEG recordings, ictal onset zone, seizure semiology and surgical outcome were compared.

Results: Patient 1: Interictal spikes started from the left parieto-temporal region and quickly propagated to the primary and supplementary motor cortex, as revealed by analysis of the MEG data. This is concordant with the seizure semiology. ICEEG recordings with subdural grids showed a misleading ictal onset zone at the propagated site. MEG-directed review of the patient's high-resolution MRI revealed a subtle cortical malformation in the posterior insular/parietal opercular region, the resection of which rendered the patient seizure free.

Patient 2: MEG interictal spikes showed various propagation patterns within the insula, from the insula to the frontal operculum, and from the orbito-frontal area to the temporal pole. These findings could explain the semiologic features of her epilepsy. In this patient, evaluation of simultaneous stereo-EEG and MEG recordings confirmed the propagation pattern within the insula. Figure 1 shows the maximally involved stereo-EEG contacts coinciding with the trajectory of the moving dipole, as the latter sweeps across the insula area.

Patient 3: MEG interictal activities exhibited bidirectional propagation within the left perirolandic region. ICEEG recordings with subdural grids, however, showed a much more diffuse interictal/ictal pattern over the left centro-parietal region. No resective surgery was performed due to the lack of a clear focal onset on ICEEG and the proximity of ictal activity to the sensorimotor areas.

Conclusions: Using single dipole and minimum norm source localization methods, we are able to examine the propagation of MEG interictal activities in a spatio-temporal manner. This may help in the accurate localization of the true ictal onset zone especially in cases where interpretation of invasive recordings is difficult due to inadequate sampling.

IMAGE: images/905755_A.jpg

Figure 1. Analysis of one interictal spike of Patient 2. Sequential moving dipole fit results over 30 ms are shown in the color coded trajectory. The blue dots indicate the reconstructed stereo-EEG electrode positions. The current density reconstruction map (using the minimum norm method) is also shown with a color coded scale. All are superimposed with the patient's MRI (A. coronal; B. sagittal; C: axial) and a 3D reconstructed cortical surface (D).

2.087

GENERALIZED 3 HZ SPIKE-AND-WAVE COMPLEXES EMANATING FROM FOCAL EPILEPTIC ACTIVITY IN PEDIATRIC CASES

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Rationale: Evolution of seizures from focal spikes to generalized 3 Hz spike-wave complexes (SWC) is an uncommon electrophysiological pattern; reported, for example, in 3 patients with Gastaut type childhood occipital lobe epilepsy by Caraballo (2005). While assessing the origin of this phenomonon in a patient, it is important to distinguish secondary bilateral synchrony vs two separate epilepsy syndromes in the same patient, since the therapeutic stragegy often hinges on this distinction.

We present two pediatric patients who showed electrophysiological seizure propagation patterns that included 1) symmetrical, or bilaterally synchronous from onset SWCs, 2) focal activity which progressed to generalized 3 Hz SWC seizures. These cases illustrate the sometimes close relationship in children between a focal epileptogenic area and generalized discharges.

Methods: Case 1: A 10-year-old boy, whose seizures started at the age of 6. Seizure frequency was about 5 per day and semiology consisted of either dialeptic (absence-like) seizures or abdominal aura evolving to automotor seizures. MRI showed a small mass in the left medial temporal structures, which was subsequently resected (see Figure).

Case 2: A 9 year-old girl, whose seizures started at the age of 5, and became intractable by the age of 7 years. The patient had a history of very frequent dialeptic seizures ranging from 5 to 100 per day. Development and neuropsychological function were within the expected range for the patient's age. MRI was normal, but ictal SPECT scan showed areas of hyperperfusion in the left superior and middle temporal gyrus.

Results: In both of these cases, the EEG showed 1) synchronous generalized 3Hz SWC, characteristic of typical absence seizures, and 2) unusual secondarily generalized 3 Hz SWC seizure patterns, which initially arose from the left temporal region. In addition both patients showed focal spikes in the left temporal region, and at times both temporal regions. Patient 1 was rendered seizure-free (follow-up period of 29 months) following resection of the mass lesion, pathologically-confirmed as a ganglioglioma. Postoperative EEGs no longer showed focal or generalized epileptiform abnormalities.

In case 2, magnetoencephalopgraphy (MEG) localized the spikes to the left superior and mid-temporal gyrus. This patient was not offered resective epilepsy surgery due to proximity of the putative epileptogenic area to eloquent (language) cortex.

Conclusions: The disappearance of SWC and the corresponding dialeptic seizures after a small resection in case 1 confirms that the unusual evolution of this patient's seizures was indeed secondary bilateral synchrony. MEG results in case 2 also render support to the hypothesis of a focal onset with secondarily generalized SWC.

These cases illustrate the complex and sometimes surprising interactions between generalized and focal epileptogenic tendencies. Employing multiple modalities to sort out these interactions can produce a successful therapeutic strategy.

IMAGE: images/904859_A.jpg

2.088

A CASE-REPORT USING HIGH PRECISION, NAVIGATED TRANSCRANIAL MAGNETIC STIMULATION

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Rationale: To study cortical representation of upper and lower extremity-muscles in a 16 year old boy to optimize planning of epilepsy surgery.

Methods: The boy was born with a transposition of the great arteries. At 2 days, he suffered massive left sided ischemic cerebral damage. This lead to a right hemiparesis. From six years of age he suffered from therapy-resistant epilepsy. Preoperative investigations (v-scalpEEG, dipoleanalysis and SPECT) indicated a right frontal focus. fMRI could not produce any activity in the left hemisphere. Due to widespread damage on the left side, findings were interpreted as rapid spread from left to right and a left mesial frontal resection was performed. Six months postoperative seizures reappeared. Navigated transcranial magnetic study (NBS) was performed to decide if another left sided resection was possible. Using NBS (Eximia, Nexstim Ltd), the cortical representation of upper and lower extremity muscles was investigated.

Results: The NBS investigation could define cortical representation of extremity muscles. Hand and upper arm muscles of left side had normal somatotopic localisation in right primary motor area (M1). Control of the right hand muscles was shifted to corresponding area in the right hemisphere. Right forearm muscles were governed bilaterally from M1. Control of the right leg was unaltered in the left M1.

Conclusions: Using NBS, localisation of the cortical control of different muscles can be investigated with high precision. In this case, a partial contralateral transfer of motor function of a forearm muscle was demonstrated.

2.089

IDENTIFYING PATHOLOGICAL AND FUNCTIONAL NETWORKS WITH SINGLE PULSE ELECTRICAL STIMULATION IN PATIENTS WITH INTRACTABLE EPILEPSY

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Rationale: Epileptic areas in pre-surgical evaluation of epilepsy patients are usually identified by visual inspection of the electro-corticogram. Recent studies suggest that single pulse electrical stimulation evoked late potentials (SPES) correlate with the seizure onset zone. We tried to reproduce this finding by systematically stimulating all electrodes over the presumed epileptic area. Furthermore, we investigate if SPES can be used to identify not only pathological but also functional networks, such as the ones involved in language.

Methods: We performed systematic bipolar stimulation of all electrodes by administering a single pulse electrical current (10mA, 0.5Hz, 0.2msec pulse width, 20 trials per electrode pair) on four patients undergoing intracranial monitoring for intractable epilepsy. Electrodes were localized using post-operative CT and MRI and aligned upon the reconstructed cortical surface of a pre-operative MRI scan. Responses to electrical stimulation were averaged at all electrodes. The stimulation response at each electrode was considered significant if the late response (100-1000ms) exceeded ±3 standard deviations from the baseline activity (-500 to 0ms). Language areas were identified using standard functional stimulation mapping.

Results: Stimulating electrodes over Broca's area in two patients showed significant responses in other electrodes considered part of the language network as defined with functional stimulation mapping. Responses to stimulation in the seizure onset zone were mainly found in electrodes over well circumscribed areas involved in seizure onset and early spread.

Conclusions: Our results suggest that single pulse electrical stimulation evoked potentials correlate reasonably well with clinically defined epileptic areas. Furthermore, the same method might prove to

be useful to not only delineate pathological but also functional networks. We believe that single pulse cortico-cortical electrical stimulation is a promising technique in delineating the seizure onset zone and eloquent cortex.

2.090

ALTERED CORTICAL EXCITABILITY IN DRUG-NAïVE GENERALIZED OR FOCAL EPILEPSY PATIENTS

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Rationale: The cortical silent period (CSP) findings in patients with epilepsy are variable. A lengthened CSP was found in untreated patients with idiopathic generalized epilepsy (IGE). However, normal CSP was reported in patients after a first-ever generalized seizure, patients with progressive myoclonic epilepsy, juvenile myoclonic epilepsy, and cryptogenic partial epilepsy (PE). In this study, we used transcranial magnetic stimulation (TMS) to investigate the difference of cortical excitability between patients with IGE or PE and normal controls.

Methods: we consecutively recruited 175 drug-naïve patients with epilepsy (IGE 55, PE 120, mean age 29.1 yrs) and 80 age- and sex-matched normal subjects with no drug history for CNS. Based on the seizure semiology, EEG, and brain MRI, epileptic focus was lateralized into right (N=65), or left hemisphere (N=55) in PE patients. We measured TMS parameters including resting motor threshold (RMT), motor evoked potential (MEP) amplitudes, cortical silent period (CSP), intracortical inhibition (ICI, interstimulus interval 2-5ms) and facilitation (ICF, interstimulus interval 10-20ms). The TMS parameters were measured during seizure free state more than 48 hours in patients.

Results: In IGE patients, interhemispheric differences of CSP were not found in any stimulus intensity ($P > 0.05$). However, the mean CSP was longer in IGE patients compared with normal controls at all stimulus intensities ($P < 0.05$). In PE patients, TMS parameters were compared between 1) ipsilateral hemisphere to epileptic focus (IH) vs. contralateral one (CH), or 2) IH or CH vs. normal controls, and 3) IH or CH vs. IGE patients. The mean CSP was significantly shorter in IH than that in CH at 120% and 140% of RMT ($p < 0.05$). Mean CSP duration in CH was significantly longer at the stimulus intensities 120 - 150% of RMT and that in IH was longer only at 120% of RMT than that of normal controls ($p=0.005$). Between PE and IGE patients, there were no significant differences of CSP at any stimulus intensity. RMT, MEP amplitudes, ICI, and ICF were not different among IGE, PE, and normal control groups.

Conclusions: These findings suggest that the CSP may have a lateralizing value in partial epilepsy by shorter CSP in the epileptic hemisphere. Prolonged CSP in epilepsy patients compared to normal subjects may indicate the abnormally increased interictal cortical inhibition in human epileptic brain.

2.091

CONNECTIVITY BETWEEN THE POSTERIOR CINGULATE AND MESIAL TEMPORAL STRUCTURES

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Rationale: The brain's default network is an anatomically defined system that is active during undisturbed thinking. Two of its subsystems, the medial temporal lobe (MTL), involved in memory retrieval, and the medial prefrontal subsystem, involved in construction of mental simulations, converge on the posterior cingulate (PC) cortex. While neuroimaging has demonstrated functional connectivity among these structures, our aim was to demonstrate connectivity between the PC and MTL by neurophysiological methods.

Methods: Four women (ages 23 to 58 years) with intractable nonlesional temporal lobe epilepsy underwent implantation of depth electrodes for seizure-focus localization. Implanted areas included anterior, middle, and posterior hippocampi; amygdalae; and PC. Single pulse stimulation (1 Hz, pulse width 0.3 msec, at 2-10 mA) was applied to implanted structures.

Results: Cerebro-cerebral evoked potentials (CCEPs) with early and late components were recorded bidirectionally between PC and ipsilateral hippocampus (n=3). Stimulation of PC elicited responses throughout the hippocampus, with maximal amplitude posteriorly (n=2). Stimulation of the anterior, middle, and posterior hippocampal electrodes elicited CCEPs in the PC region, with maximum amplitude upon stimulation of the posterior hippocampus (n=2), and anterior hippocampus (n=1). The location of the PC electrodes in the patient with no MTL CCEPs was different from PC electrode locations in the others.

Conclusions: Cerebro-cerebral evoked potentials (CCEPs) with early and late components were recorded bidirectionally between PC and ipsilateral hippocampus (n=3). Stimulation of PC elicited responses throughout the hippocampus, with maximal amplitude posteriorly (n=2). Stimulation of the anterior, middle, and posterior hippocampal electrodes elicited CCEPs in the PC region, with maximum amplitude upon stimulation of the posterior hippocampus (n=2), and anterior hippocampus (n=1). The location of the PC electrodes in the patient with no MTL CCEPs was different from PC electrode locations in the others.

2.092

HUMAN HIPPOCAMPAL-CINGULATE GYRAL CONNECTIVITY -CORTICO-CORTICAL EVOKED POTENTIALS(CCEP) STUDY

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Rationale: Human limbic system is not described in detail. Recent diffusion tract imaging on MRI technique enables to visualize the human fornical circuit or cingulum. However this technique demonstrates partially anatomical connectivity not functional connectivity, therefore so far nobody could elucidate limbic functional connectivity. Cortico-Cortical Evoked Potential (CCEP) method was first introduced by Matsumoto and Nair et al in 2004 (Matsumoto et al.,2004). They clearly showed the functional connectivity in human language between Broca and Wernicke area. After this report, using this technique connectivity of human cortical motor (Matsumoto et al., 2007), bilateral cortical motor (Terada et al., 2008), bitemporal connectivity (Umeoka et al., 2009) were also reported. Today this seems to be one of the established methods to ensure functional connectivity between two interest areas. The purpose of this study is to neurophysiologically clarify the functional connectivity of human limbic system with CCEP method. Especially in this study, we focused on the connectivity between hippocampus and cingulated gyrus.

Methods: We currently recruited five intractable focal epileptic patients who implanted stereoelectroencephalogam electrodes (SEEG) in brain area for exploring ictal onset area. After finishing recording interictal and ictal events, antiepileptic medications were restarted and then CCEP was performed. Electric pulse stimuli were alternatively delivered in a bipolar fashion to two adjacent SEEG contacts on hippocampus. Stimulus parameter was described in elsewhere (Matsumoto et al., 2004). Cortico-cortical evoked potentials were recorded by averaging electroencephalogram from other contacts. We did twice of each session for confirming reproducibility. This study was approved by Cleveland Clinic IRB. We obtained the informed consent from all patients in the research use. Each patient's locations of electrodes were different in each patient, therefore we selected five patients who had contacts both hippocampus and cingulate gyrus to examine the limbic connectivity.

Results: All patients showed prominent CCEP responses in cingulated gyrus compared with another surrounding cortex such as medial occipital cortex or medial part of superior parietal lobule. Especially responses in posterior part of cingulate gyrus were more obvious than other cingulate gyrus.

We could preliminary found the functional connectivity between hippocampus and posterior cingulate gyrus. For detail analysis, we should recruit more cases.

Conclusions: We could preliminary identify the neurophysiologial connectivity between hippocampus and cingulate gyrus. And the connectivity of other brain areas such as insular and orbitofrontal cortex will be investigated. This finding also leads to the understanding propagation pattern of the medial temporal lobe epilepsy, and might be clarifying of the Alzheimer's disease and psychiatric disorder such as depression or schizophrenia.

2.093

INTRACRANIAL ELECTROPHYSIOLOGICAL STUDY OF THE HUMAN POSTERIOR CINGULATE GYRUS DURING REST, SELF-REFERENTIAL MEMORY PROCESSING, AND ARITHMETIC TASKS

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Rationale: Posteromedial cortex (PMC) collectively defines an anatomical region in the primate brain that encompasses the posterior cingulate cortex, retrosplenial cortex and precuneus. Uniquely, the PMC is one of the most richly connected and metabolically active regions of the cerebral cortex. Moreover, the PMC is thought to be involved in higher order self-referential cognition and plays a key role in correlated brain network activity observed during the resting state. The current intracranial electrophysilogical study addressed the resting and task-dependent patterns of activity within the PMC and lateral parietal cortex (LPC).

Methods: Electrocorticography (ECoG) recordings were performed in five patients with refractory epilepsy implanted with multiple strips and grids over the medial cortical surface. Prior to implantation of electrodes, all subjects had undergone routine fMRI studies during the resting state. Intracranial electrophysiological data were acquired during a cognitive task that included math equations (MATH task) or statements about themselves (SELF condition) or about a distant other person (NON-SELF condition). Subjects were instructed to respond via button presses as to whether each equation or statement was true or false. Math and Self/Non-Self stimuli were separated randomly from each other by the REST condition where subjects passively viewed a fixation cross that appeared on the screen for 5 seconds. Subjects were instructed to "let their mind wander" during the REST condition. Conditions were presented randomly and were counterbalanced. The total time of the experiment varied by the reaction time of the subject during MATH, SELF, and NON-SELF conditions.

Results: Our findings can be summarized as follows: 1) The PMC showed a significant increase of broadband gamma activity (40-180Hz) during the resting state while the activity in the same frequency range was decreased significantly during arithmetic task; 2) the LPC showed a significant increase of gamma

activity during the arithmetic task while the activity in the same frequency range was not seen during the resting state; 3) in the PMC or LPC, when there was an increase in the gamma power during a task, there was a parallel decrease of activity in the lower frequency range (e.g, alpha band activity)

and vice versa; 4) there was a significant increase of activity in the gamma range within the retrosplenial cortex during autobiographical statements; 5) electrical brain stimulation within the PMC did not cause any perceptual or behavioral change.

Conclusions: The superior spatial and temporal resolution of the ECOG method allowed us study some of the remaining questions about the functional role of the PMC and the temporal dynamics and the exact anatomical specificity of resting or task dependent activity within the PMC.

2.094

MONOPOLAR VERSUS BIPOLAR ELECTRICAL STIMULATION FOR EXTRAOPERATIVE CORTICAL MAPPING IN PATIENTS WITH FOCAL EPILEPSY

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Rationale: Extraoperative cortical stimulation is used to identify eloquent cortex in patients undergoing invasive investigations. However, it is not standardized across centers. In some, adjacent pairs of electrodes are stimulated (bipolar stimulation), requiring to stimulate each electrode twice with different adjacent electrodes to identify the function underlying each electrode. In other centers, one electrode is stimulated, referenced against a distant electrode (monopolar stimulation). We aim to compare the two methods for mapping results, tolerability and ease of application.

Methods: Four patients with refractory frontal lobe epilepsy (3 left, 1 right) were enrolled. The study was approved by the hospital ethics committee and informed consent obtained. Stimulation followed reinstatement of antiepileptics, starting away from the ictal onset zone, with stepwise increase of stimulus intensities (in 2 mA increments, maximum of 15mA). Bipolar stimulation was performed with first horizontal adjacent electrodes, then vertical as is practice in our center

Results: A total of 417 electrodes/electrode pairs were stimulated (279 bipolar, 138 monopolar). 249 cortical stimulations resulted in clinical signs, with comparable stimulation intensity (Table1). Anatomical mapping results were similar but not identical: 71 electrodes were over eloquent cortex using bipolar stimulation, 76 using monopolar. 7

electrodes showed motor signs using monopolar stimulation only, two with bipolar stimulation only.

The percentage of electrodes/ pairs exhibiting afterdischarges (ADs) and their duration was comparable. Stimulation sessions were performed over 2 days in 3 patients; in one patient it was completed in one day, with an increase in ADs in the third hour of stimulation (monopolar). When analyzing the 3 patients with sessions on separate days, monopolar stimulation showed significantly fewer ADs (Chi Square test, $P<0.05$). Bipolar stimulation required more time (124+ 34min versus 57 +17min) and a brief final analysis, monopolar results are available immediately.

Conclusions: Results of mapping identified similar anatomical areas as eloquent cortex, but were not identical. Monopolar stimulation identified a slightly larger area as eloquent. Some possible advantages of monopolar stimulation emerged: 1. Results are available quicker; 2. Our small sample did not reveal any definite differences in percentage or duration of afterdischarges; prolonged stimulation in one session may have marred results in one patient. In patients stimulated on 2 days, the percentage of afterdischarges appears lower using monopolar stimulation. This needs to be confirmed in a larger sample.

Table 1

IMAGE: tables/901274_T1.jpg

NS:not significant; SD: standard deviation.

2.095

PERCEPTUAL AND BEHAVIORAL PHENOMENA DURING ELECTRICAL STIMULATION OF THE HUMAN BRAIN

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Rationale: An overview of the electrical brain stimulation (EBS) reports is missing from the current literature. Such an overview would provide useful information about symptomatogenic zones in the brain of patients with epilepsy.

Methods: Using PUBMED, we searched for publications containing the keywords “human”, “brain”, “stimulation”, or “epilepsy”, which resulted in 9272 reports. We scanned the abstract of all reports and selected 109 reports that were published in English and dealt with EBS in human subjects. We also searched for relevant papers in the references provided in each of these publications and reviewed additional books and magazine articles.

Results: An abridged summary of the general themes of our findings is as follows: 1. Frontal Lobe: eye movements, change of posture and tone, oroalimentary automatisms, emotional facial expression and laughter, reaching, grasping, and nonconscious movements; retrosternal pain or discomfort, disequilibrium, somatic sensations; speech arrest, reading, singing problems, palilalia; dysautonomia. 2. Insula: sensation of suffocation, bilateral pain, warmth and or cooling sensation, vertigo, nausea, feeling of falling; automatisms. 3. Parietal Lobe: somatotopic sensation, vestibular and sensorimotor responses and visual disturbances, urge to move or illusion of moving body parts, out of body experience, hemispatial neglect, somatosensory and vestibular sensations, anomia, speech arrest and conduction aphasia, finger agnosia and acalculia. 4. Occipital Lobe: Mostly in calcarine, occipitoparietal and occipitotemporal areas: simple visual sensations such as seeing simple patterns, geometric shapes, phosphenes, colors, movement; visual hallucinations such as seeing people and or movements, visual illusions such as slowing down of actual

movements. 5. Temporal Lobe: Feeling of unreality or familiarity; emotional feelings and recall of past experiences; auditory hallucinations, pain or automatisms; visual hallucinations; disruption in reading, comprehension, naming and or identification (left inferior). 6. Subcortical Areas: (STN or internal capsule): transient acute depression, hypomania; motor responses such as crying, psychomotor retardation, exaggerated facial and gag reflexes; language impairments; autonomic changes; and eye apraxia.

Conclusions: This review was an attempt to bring to light some of the classic EBS studies, classify the evidence in a systematic way, and provide details about the parameters used in each reported study. Findings of EBS studies must be interpreted cautiously in the light of variables such as the location of the brain target verified or presumed, the strength of electrical charge delivered, and the mode of electrical stimulation (i.e., bipolar or unipolar).

2.096

STIMULATION BASED PARADIGM FOR ASSESSMENT OF EPILEPTOGENIC POTENTIAL

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Rationale: Our previous work has shown that by stimulating the brain with specific patterns of either sensory or direct electrical pulses, the so called “carrier frequency” paradigm, we are able to assess the ability of the system to generate epileptiform activity and eventually seizures. Computer model studies have shown that this effect can be explained on the basis of response properties of the neural network to stimulation and can account for multiple parameter-driven transitions to an epileptic seizure. We have reported on a, proof-of-principle, clinical application of this technique in patients undergoing pre-surgical evaluation with implanted electrodes both to localize the seizure onset site (SOS) and to indicate the time periods when seizures can be anticipated.

The present contribution refines the carrier frequency modulation concept and excludes possible linear interference from volume conductance and/or stimulus artifacts while affording further statistical confirmation of our analysis technique based on the epileptogenic potential quantity called relative phase clustering index (rPCI).

Methods: We applied a new, improved approach towards identifying the SOS in five patients and in an extra one to estimate the time of upcoming seizure. We used (1) bi-phasic cyclic alternating polarity stimulation sequences (BiCAP) and (2) bipolar EEG traces to compute rPCI . This improved approach excludes the influence of linear effects either from the stimulus or from the neural response. It also reduces possible influences from any common electrical reference.

Results: We achieved correct SOS localization in all five cases, including an MRI-negative case in a patient with previous unsuccessful resection. The results of the long-term rPCI monitoring support the hypothesis that the seizures are associated with a bilateral increase of the rPCI.

Conclusions: The study confirms our concept of fluctuation-driven transitions to epileptic seizures where only probabilistic predictions of the time of the seizure are possible. It also shows that non-linear neuronal dynamics account for the high rPCI values at the SOS. Our results warrant the use of rPCI as an identifier of seizure vulnerability and its possible use for state-dependent therapeutic approaches aiming at arresting epileptic seizures.

2.097

INTELLIGENCE RELATES TO STRUCTURAL INTEGRITY OF NORMAL APPEARING WHITE MATTER IN TUBEROUS SCLEROSIS COMPLEX

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Rationale: To study the relation between intelligence and diffusion tensor imaging (DTI) characteristics of normal appearing white matter (NAWM) in children with tuberous sclerosis complex (TSC).

Methods: In 26 children with clinically definite TSC intelligence quotients (IQ) or developmental quotients were related to DTI characteristics of NAWM. Whole brain tractography was performed, and fractional anisotropy (FA), apparent diffusion coefficient (ADC), radial diffusivity (RD) and axial diffusivity (AD) were calculated for well-defined segments of white matter tracts. Neuropsychological examination was performed, closely in time to the MRI, to assess intelligence or developmental quotients.

Results: Corrected for age, a significant inverse correlation ($p<0.01$) was found between IQ and ADC in mesiotemporal, frontal and occipital NAWM tracts. In addition, IQ correlated positively with FA in corpus callosum and fronto-occipital tracts. In all supratentorial commissural and association tracts RD was inversely correlated with IQ ($p<0.01$).

In summary, DTI characteristics of infratentorial tracts and ascending or descending projection fibers showed no correlation with intelligence, as compared with supratentorial association and commissural fibers.

Conclusions: DTI characteristics of supratentorial NAWM tracts are related to intelligence in children with TSC. These findings suggest that cognitive dysfunction is, at least partly, related to a disturbed integrity of the NAWM in TSC, reflecting widespread microstructural abnormalities of white matter that are not visible on conventional MRI. Thus, white matter architecture, and not tuberload alone, is an important determinant for intelligence, adding to our understanding of the underlying pathogenesis in TSC.

2.098

STRUCTURAL CONNECTIVITY IN PEDIATRIC EPILEPSY MEASURED WITH W-MATRIX DIFFUSION TENSOR TRACTOGRAPHY

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Rationale: Brain development of children with epilepsy is a topic of increasing interest and concern. In an ongoing study of children with epilepsy serial volumetric MRI scans demonstrate decreased rates of white matter growth [Herman.,P.D et al. Epilepsia 2010 Apr 2]. This investigation address the issue of whether structural connectivity in these children is also abnormal. If so,an important issue is whether deficient connectivity is associated with common neurobehavioral comorbidities in this population including cognitive and behavioral problems?

White matter structure is probed noninvasively by diffusion tensor tractography(DTT). DTT is more sensitive to white matter deficiencies than voxel-wise fractional anisotropy (FA) maps because deficiencies enter into DTT as multiplicative factors while they enter into FA maps linearly. We have developed a new form of DTT called W-matrix tractography (WMT) that is more robust than conventional DTT because it allows for multiple branching from every voxel of every fiber tract [Lee.,J.E. et al Neurology 2008; 70(Suppl):A2]. Here we examine the utility of WMT for studying epilepsy in children.

Methods: Study participants are 8 to 18 years of age with controls chosen from age-matched first-degree cousins. Participants undergo serial neuropsychological testing and diffusion tensor imaging (DTI). For each subject, a W-matrix is constructed from DTI data. Each element W(i,j) is a product of 3 factors:(1)a product of the FA's of voxels i and j; (2)a structure factor related to the alignment of the first principal DTI eigenvectors from these two voxels;and(3)a distance factor that decreases with distance between the voxels.Each W(i,j) is a number between 0 and 1, with 0 representing no connectivity and 1 reflecting optimal connectivity.WMT can be implemented in two ways.In the first,an arbitrary seed region of interest is chosen. A neural net simulation is then performed with the W(i,j)'s interpreted as transition probabilities. The simulation is continued until a stable spatial pattern of activation is obtained. The spatial distribution of this pattern then represents those brain regions that are connected to the seed region of interest. The second approach involves calculating the eigenvalues and eigenvectors of W. The eigenvectors and eigenvalues respectively represent the spatial distribution and strength of brain connectivity.

Results: To date,we collected DTI scans from 5 children with epilepsy and 10 controls.With a seed voxel in the splenium midline, W-matrix neural net simulation converges to steady state in about 100 time steps(Fig.1). Spatial distributions at steady state in Fig.2 shows that the seed voxel is connected to fewer other voxels in children with epilepsy compared to healthy controls.

Conclusions: W-matrix tractography is computationally feasible in children with epilepsy and controls and promises to provide unique information regarding structural abnormalities. The finding here suggest decreased connectivity in children with epilepsy with seed voxel in the splenium.

IMAGE: images/889023_A.jpg

Steady state convergence of network simulation

IMAGE: images/889023_B.jpg

2.099

HIPPOCAMPAL ATROPHY IN PATIENTS WITH MEDIAL TEMPORAL LOBE EPILEPSY: DIFFERENCES BETWEEN THE 'GENERATOR' AND THE 'RECEIVER'

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Rationale: Hippocampal sclerosis (HS) is traditionally considered to be the cause of seizures in patients with medial temporal lobe epilepsy (MTLE). HS can be observed in routine brain MRI as hippocampal atrophy. However, some patients with unilateral MTLE exhibit mild contralateral hippocampal atrophy. Atrophy in the hippocampus with HS (the 'generator' of seizures) is considered to be a consequence of cell death with formation of aberrant epileptogenic neuronal circuitry, whilst the contralateral hippocampus is atrophied possibly as a consequence of the excitotoxic effects of seizures without epileptogenic reorganization. The distinction between the epileptogenic hippocampal atrophy of HS (the 'generator'), versus the non-epileptogenic atrophy (the 'receiver) may enable the correct identification of the seizure onset site and lead to better surgical results. This study aimed to compare the tridimensional distribution of hippocampal atrophy in the ipsilateral and contralateral hippocampi of patients with MTLE.

Methods: We studied 14 patients with MTLE (6 with right and 8 with left MTLE) with unilateral seizure onset documented by video-EEG corresponding to the side of hippocampal atrophy. All patients were submitted to unilateral hippocampal resection with hippocampal sclerosis confirmed by histology. Importantly, all patients were seizure free at least 12 months after surgery. We also studied a control group of 34 healthy individuals. T1-weighted images were submitted to voxel-based morphometry preprocessing and analysis of the hippocampus through cytoarchitectonic regions of interest (ROIs). The hippocampi of patients and controls were compared employing a non-parametric voxel-wise Wilcoxon test. Results were corrected for multiple comparisons with the application of an FDR corrected threshold for $q<0.05$.

Results: Patients with left MTLE showed atrophy within both hippocampi, but the atrophy within the ipsilateral hippocampus (both for left and right MTLE) was more intense and more widely distributed (Figure 1). The anterior-inferior aspect of the head of the hippocampus was the site of more significant damaged in the ipsilateral hippocampus (Figures 1 and 2) (site of maximal atrophy: Left MTLE, left hippocampus x=-28, y=-16, z=-24, Z=3.6; Right MTLE, right hippocampus x=22, y=-11, z=-27, Z=2.9). On the contralateral hippocampus, the atrophy was more noticeable in the posterior head and body areas (Left MTLE, right hippocampus x=25, y=-17, z=-21, Z=2.1; Right MTLE, left hippocampus x=-27, y=-19, z=-17, Z=2.1). There were no areas of increased gray matter volume in patients compared with controls.

Conclusions: In this study, we demonstrated that the hippocampal atrophy observed in the hippocampus that generates seizures (the 'generator') has an anatomically distinct pattern compared to the atrophy of the contralateral hippocampus (the 'receiver'). This was demonstrated on patients who achieved seizure freedom with surgery, thereby eliminating the possibility that the contralateral hippocampus may also be a site of epileptogenesis.

IMAGE: images/907168_A.jpg

The site and extent of hippocampal atrophy in patients with MTLE. The scale bar represents Z scores.

IMAGE: images/907168_B.jpg

Note the predominance of antero-inferior atrophy in the ipsilateral hippocampus. The scale bar represents Z scores.

2.100

LANGUAGE LATERALIZATION DETERMINED BY TRACT-BASED SPATIAL STATISTICS OF THE ARCUATE FASCICULUS

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Rationale: The purpose of this study was to utilize diffusion tensor imaging (DTI) and Tract-Based Spatial Statistics (TBSS) to evaluate the relationship between language laterality in epilepsy patients measured by the Wada test with asymmetry in measures of fractional anisotropy (FA), of major white matter language tracts. The Wada test is the current gold standard for determining language laterality, but is invasive and costly. Functional imaging techniques require compliant patients, are time-consuming and susceptible to interpretation bias. We have previously shown that it is possible to create a logistic regression model that uses patient handedness, fMRI and arcuate fasciculus (AF) DTI data together to predict language laterality (Ellmore 2010) In this report we try to use TBSS alone for this purpose.

Methods: Whole-brain diffusion-weighted images (32-direction, 3T) were obtained on 18 patients without prior resections, scheduled to undergo Wada testing. Individual diffusion-weighted images were non-linearly aligned and transformed into standard patient space using TBSS with a 5mm full-width half maximum (FWHM) variance smoothing (Smith 2006). A group mean FA-skeleton was then constructed from the averaged FA maps. A language dominant minus non-dominant skeleton comparison was made between the hemispheres of the warped individual brains and a one sample t-test for mean > 0 was performed. Voxels were then thresholded for $p < 0.01$ and voxels of interest in the superior longitudinal fasciculus portion of the AF, were selected for generating a volume of interest (VOI). Symmetric VOIs sampled AF regions in both hemispheres. A voxel-based analysis of FA in the native patient space and computation of a laterality index (LI) where LI = [(Left average FA - Right average FA) / (Left average FA + Right average FA)] * 10 was then carried out.

Results: Wada testing revealed that 14 patients had L sided language and 4 patients had R sided language). Of these 18 patients, our method predicts Wada laterality outcome in 15, the remaining three were non-classifiable (LI of -1 to 1). This analysis shows that an area of language dependant, very significant hemispheric white matter asymmetry exists in the superior longitudinal fasciculus (SLF). Probabilistic tractography constrained by the VOI in individual patient space demonstrates that this contributes to the SLF portion of the AF.

Conclusions: Based upon this study, we conclude that DTI and TBSS may be a useful tool for predicting language laterality in patients with epilepsy. The availability of DTI makes this method easy to carry out. Future exploration includes extending this measure of analysis to other white matter markers of integrity including mean diffusivity, extending this method to patients who have cortical stimulation mapping and confirmation of the finding in larger numbers.

Ellmore TM, et al. Temporal lobe white matter asymmetry and language laterality in epilepsy patients. Neuroimage. 2010 49(3).

Smith SM, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage. 2006 31(4).

IMAGE: images/908320_A.jpg

Figure 1: Average FA map, with symmetrical white matter skeleton and thresholded VOI for laterality present in the SLF.

IMAGE: images/908320_B.jpg

Figure 2: Chart demonstrating LI = (L avg FA - R avg FA) / (L avg FA + R avg FA) * 10. Demonstrates that laterality was significantly predicted in 15 of the 18 patients with both L and R lateralized language.

2.101

REORGANIZATION OF THE RIGHT ARCUATE FASCICULUS FOLLOWING LEFT ARCUATE FASCICULUS RESECTION IN CHILDREN WITH INTRACTABLE EPILEPSY

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Rationale: Recent studies have shown reorganization of language networks in patients with temporal lobe epilepsy. However, these studies were cross-sectional. We addressed the reorganization of language network longitudinally using diffusion tensor imaging (DTI), an MRI method that allows the assessment of white matter microstructure and integrity in vivo. In the present study, we evaluate the right arcuate fasciculus (rARF) following resection of the left ARF (lARF) in children with intractable epilepsy.

Methods: We selected 10 children with intractable epilepsy whose resections included the lARF and who had DTI-MRI scans at both pre-surgery and post-surgery timepoints (age at pre-surgery scan: 4.75 +/- 3.72 years; age at post-surgery scan: 5.60 +/- 3.63 years; duration between surgery and post-surgery scan: 0.62 +/- 0.35 years; 5 males). Tensor calculation and tractography were performed using DTI Studio (Jiang H et al., Comput Methods program Biomed 2006;81:106-16) with starting and ending FA threshold values of 0.2. Right ARF on both pre-surgery and post-surgery scans were isolated using a protocol described previously (Sundaram SK et al., J Pediatr 2008;152:250-5). The morphological appearance and the mean FA values of the isolated rARF fiber tracts were evaluated.

Results: A repeated measures analysis of the rARF showed a significant ($p = 0.051$) increase in the mean FA values for the post-surgery scans (0.446 +/- 0.008) compared to the pre-surgical scans (0.416 +/- 0.011) after controlling for age. Furthermore, the change in FA values of the rARF from pre-surgery scan to post-surgery scan showed a near significant positive correlation with duration between lARF resection and post-surgical scan (Pearson's $r = 0.59$; $p = 0.07$). In addition, 8 out of the 10 children showed marked enlargement of the right ARF postsurgically (see Figure 1).

Conclusions: Our results show an increase in the FA values and morphological enlargement of the rARF following resection of lARF in children with intractable epilepsy. These findings suggest a compensatory reorganization in the rARF beyond the age-related maturational changes, presumably triggered by resection of the lARF.

IMAGE: images/906737_A.jpg

Figure 1: Sample cases showing enlargement of the right arcuate fasciculus (rARF) from pre-surgery scan to post-surgery scan. The duration between surgery and post-surgery scan for subject 1 was 0.62 years and for subject 2 was 0.45 years.

2.102

MAPPING THALAMIC PATHOLOGY IN IDIOPATHIC GENERALIZED EPILEPSY AND TEMPORAL LOBE EPILEPSY

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Rationale: The thalamus plays a pivotal role in the epileptogenic network of both idiopathic generalized epilepsy (IGE) and temporal lobe epilepsy (TLE). Our purpose was to assess the local structural changes in the thalamus in IGE and TLE in vivo.

Methods: We obtained manual thalamic segmentations on MRI in 37 patients with drug-resistant TLE, 18 patients with IGE (11 epilepsy with generalized tonic-clonic seizures only, 7 juvenile myoclonic epilepsy, and 1 juvenile absence epilepsy), and 19 age-and sex-matched healthy controls. In each individual, we obtained surface-based measurements of local deformations (SPHARM-PDM, Styner et al. 2006) of the thalamus relative to a template model. We assessed differences in thalamic SPHARM-PDM in each patient group relative to controls, as well as the effects of clinical variables using linear models.

Results: Relative to controls, TLE patients displayed local atrophy mainly in ipsilateral anterior, mediodorsal, and pulvinar thalamic subdivisions (Figure A and B). In TLE, atrophy intensified with a longer duration of epilepsy (-0.01 mm/year, $t=-3.17$, $p<0.005$) and a previous history of febrile convulsions ($t=-1.87$, $p<0.08$). IGE patients showed diffuse and bilateral tendencies for local thalamic atrophy ($p<0.025$). The only change that surpassed the threshold at FDR<0.05 was observed in the right medial division (Figure C). Although there was a slight tendency for progressive atrophy in this cluster, this effect was not significant ($t=-1.31$, one-tailed $p=0.10$). However, post-hoc power analysis on the duration effect size in the cluster (power=0.95, effect size $|r|=0.56$, alpha=0.05, one-tailed) indicated that we would have needed a total sample size of 26 IGE patients to detect significant progressive thalamic atrophy. We did not find any difference in local volume between patients with juvenile myoclonic epilepsy and those with generalized tonic-clonic seizures only (FDR>0.2).

Conclusions: The medial thalamic division is the most affected structure in both TLE and IGE. In the former, atrophy is more widespread and ipsilateral to the seizure focus.

IMAGE: images/907763_A.jpg

2.103

THREE-DIMENSIONAL CAUDATE ATROPHY PATTERN IN RECENT-ONSET JUVENILE MYOCLONIC EPILEPSY

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Rationale: The basal ganglia play an important role in the modulation and propagation of seizure activity. Recent neuroimaging studies have found that caudate volumes are reduced in juvenile myoclonic epilepsy. However, the precise location of atrophy pattern within the caudate nucleus has not been studied. The goal of the current study is to define the distribution of caudate atrophy in recent-onset JME. Using three-dimensional shape analysis, the study aims to test two competing hypotheses. On one hand, if the overall pattern of volume reduction in JME is nonspecific, then the distribution of caudate atrophy would be spread throughout the nucleus. On the other hand, if the caudate atrophy pattern reflects disruption of specific frontostiatal circuits, then atrophy should be localized to specific regions of the caudate.

Methods: T1 weighted SPGR images were obtained on a 1.5 Telsa GE Signa scanner in 21 individuals with recent-onset JME (age = 15.8 +/- 3.0 years; epilepsy duration = 8.5 +/- 3.7 months) and 54 healthy controls (HC, age = 13.3 +/- 3 years). Automated segmentation of the caudate nucleus was performed using FIRST (part of FSL, http://www.fmrib.ox.ac.uk/fsl)), which is a model-based segmentation tool that searches through linear combinations of shape modes of variation for the most likely shape, based on T1 image intensity. First, the automated segmentation process produces binarized masks of each subject's caudate nucleus. Total caudate volumes from each subject were calculated from these masks and then normalized to total intracranial volume (TIV). Second, the automated segmentation also generates a deformable mesh of vertices composed of a set of triangles. The relative position of each corresponding vertex is then compared between JME subjects and healthy controls in order to determine the specific regions of atrophy. A one-tail t-test was performed to compare TIV normalized caudate volumes between JME and HC subjects. Caudate three-dimensional shape analysis was carried out using F-statistics and multiple comparisons were corrected with false discovery rate.

Results: Individuals with JME had significantly smaller bilateral caudate volumes when compared to HC (Left 5064 +/- 361mm^3 vs. 5368 +/- 570, p=0.026; Right 5318+/-502 vs. 5631+/- 594; p=0.036). Three-dimensional shape analysis showed atrophy is located predominately in the head and body of the caudate nucleus. After correcting for multiple comparisons, the most consistent region of atrophy was located in the left dorsal and ventromedial head of the caudate.

Conclusions: The current study demonstrates that caudate atrophy in JME is selective for dorsal and ventromedial head of the caudate. These two regions have critical connections to the dorsolateral and orbital prefrontal regions, areas that are important for executive functioning and mood regulation as well as seizure propagation. Further, disturbances in frontostriatal circuits are evident in this group of JME with very recent onset seizures, suggesting that caudate atrophy is less likely due to cumulative effects of seizures.

IMAGE: images/904066_A.jpg

2.104

STEREOTACTIC AMYGDALOHIPPOCAMPECTOMY FOR THE TREATMENT OF MESIAL TEMPORAL LOBE EPILEPSY: GOOD CLINICAL SEIZURE OUTCOME DESPITE OF ONLY PARTIAL VOLUME REDUCTION OF THE TARGET STRUCTURES

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Rationale: Mesial temporal lobe epilepsy (MTLE) is the most surgically amenable epilepsy diagnosis and the results of epilepsy surgery are clearly superior to prolonged medical therapy. Stereotactic radiofrequency amygdalohippocampectomy (SAHE) is an alternative therapy of MTLE. In our hospital SAHE has been used since 2004. We produced lesions from the occipital access with a single trajectory in the long axis of amygdalohippocampal complex (AHC) using the probe with a flexible active tip. The aim of this study was to correlate volume reduction of the target structures / the hippocampus, the amygdala, entorhinal (EC) and perirhinal (PRC) cortices/ with the clinical seizure outcome.

Methods: We included 26 consecutive patients, who underwent SAHE using Leksell stereotactic system. MRI volumetry of hippocampus, amygdala, EC and PRC was performed 1 year after the procedure. The clinical outcome was assessed 1 and 2 years after the procedure according to Engel's Classification.

Results: 21 patients had left-sided and 5 patients right-sided MTLE. No serious adverse events occurred after the procedure. One year after procedure, the hippocampal volume decreased by 55.5 ± 18.0%, the amygdalar volume decreased by 49.2 ± 16.8 %, PRC volume decreased by 45.9 ± 16.7% and the size of EC decreased by 55.5 ± 19.6 %. Clinically, 1 year after the procedure 19 (73%) patients were classified as Class I, 5 (19%) patients as Class II and the treatment failed in 2 patients. The latter 2 patients were re-operated and excluded from the second year of the clinical follow-up. Two years after the procedure, 24 patients were evaluated; 19 (79%) of them were classified as Class I and only 5 (21%) patients as Class II. No statistically significant relation of target structures volume reduction and of the clinical outcome was found.

Conclusions: We have not found any significant relation between morphological changes and clinical outcome. According to our data, it seems that the attempt to make (stereotactic) MTLE surgery as radical as technically possible must not be tenable. SAHE caused only partial destruction of the target structure, but the clinical seizure outcome is very promising, two years after the procedure is comparable with classical surgical approaches.

2.105

IMPAIRED FRONTO-STRIATAL CONNECTIONS ARE ASSOCIATED WITH EXECUTIVE DYSFUNCTION IN TEMPORAL LOBE EPILEPSY

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Rationale: In addition to memory impairments, deficits in executive functioning are common in individuals with temporal lobe epilepsy (TLE), including impairments in attention, abstraction, and problem-

solving ability. Functional neuroimaging studies have found that frontostriatal circuits are critical for executive functioning. Using diffusion tractography, the current study aims to test the hypothesis that the strength of frontostriatal connections are linked to executive functioning in TLE.

Methods: Nine left TLE subjects (age 37.7 +/- 4.0 yrs [mean +/- SEM]) underwent 3 Tesla MRI scanning including high resolution DTI (64 non-collinear directions, b value = 800 s/mm2) and T1-weighted MP-Rage scans (sense coils 2.4, TR 8.4 ms, TE 3.7 ms) as well as Trails Making Tests. DTI tractography was performed using FSL (http://www.fmrib.ox.ac.uk/fsl/) to determine the relative strength of connections between the caudate nucleus and four prefrontal regions (dorsal prefrontal, ventrolateral, anterior cingulate, and lateral orbitofrontal cortex) in each hemisphere. First, caudate and prefrontal regions were segmented using Freesurfer (http://surfer.nmr.mgh.harvard.edu/). Second, these segmented regions were registered to the FA map generated in FSL using FLIRT. Third, probabilistic tractography was performed to assess for mean percent of connections between the caudate and each prefrontal region. Finally, statistical testing for correlations between mean percent of connections of in each prefrontal region and Trails A, B scores was performed using Spearmans rho and corrected for multiple comparisons (Bonferoni corrections, $p < 0.05/8 = 0.006$).

Results: Mean percentage of connectivity between the left caudate nucleus and the left dorsal prefrontal cortex was negatively correlated with Trials B making time ($r = -0.88$, $p = 0.0016$). Specifically, lower connectivity between left caudate and dorsal prefrontal was associated with slower Trials B test completion time (Figure). No other significant correlations were found between Trails B test and other prefrontal regions. In addition, there were no significant correlations between Trails A scores and mean percentage of connectivity to any prefrontal regions.

Conclusions: The current study demonstrates that altered connectivity between caudate and dorsal prefrontal cortex is associated with impaired executive functioning in TLE. It is important to note that this structural-functional relationship is selective for the dorsal prefrontal cortex, an area critical for executive functioning. Furthermore, this relationship was only significant for Trails B Making Test, a task that is more specific to executive functioning, and not Trails A Making Test, which is predominantly influenced by motor control. Finally, the impairment is lateralized to the side of seizure onset, suggesting that the epileptogenic zone may disrupt extra-temporal connections that mediate executive functioning. Taken together, the current study demonstrates that aberrant frontostriatal connectivity may serve as a mechanism for altered executive functioning in individuals with TLE.

IMAGE: images/904032_A.jpg

Mean percentage of connectivity between the left caudate nucleus and the left dorsal prefrontal cortex was negatively correlated with Trials B making time.

2.106

APPLICATION OF TRACTOGRAPHY TO DELINEATE THE RELATIONSHIP OF THE OPTIC RADIATION TO EPILEPTOGENIC LESIONS PRIOR TO NEUROSURGERY

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Rationale: Patients with drug refractory focal epilepsy may benefit from neurosurgical treatment. A major concern is to avoid causing new deficits. In patients with temporal lobe epilepsy, diffusion tensor imaging tractography can delineate the optic radiation and predict the risk of a visual field deficit resulting from anterior temporal lobe resection. A smaller group of patients have epileptogenic lesions lying in proximity to the presumed course of the optic radiation as it passes posteriorly to the occipital cortex. Conventional MR imaging does not delineate the optic radiation, so the risk of surgery cannot be predicted, nor can surgery be tailored to minimise the risk.

Methods: Conventional structural MR images and diffusion tensor imaging were acquired in 16 patients with lesions lying in proximity to the optic radiation. A probabilistic tractography algorithm was used to delineate the optic radiation and generate a map of connection probabilities. The diffusion data were co-registered with the structural data (T1 volumetric, T2 FLAIR) to demonstrate the relationship between the optic radiation and the lesion. Results were validated using postoperative visual fields and repeat imaging to look at outcome.

Results: The relationship between the epileptogenic lesion and the optic radiation was demonstrated in each patient. Visualisation as a 2D overlay on anatomical images and 3D reconstructions is demonstrated. Illustrative cases show the role of the tractography data in each part of the surgical planning process. Some patients declining surgery on the basis of risk to vision may make a different decision if better informed and the surgeon can use the information for surgical planning in those considering or awaiting surgery. Post-operative data on patients including those with and without a visual field deficit, shows a correlation of preoperative data with operative outcome.

Conclusions: Diffusion tensor imaging and tractography can demonstrate the relationship between the optic radiation and epileptogenic lesions. This is beneficial in all stages of surgical planning and correlates with outcome. Forthcoming work will aim to further reduce the risk to vision. A new interventional MR suite has been installed, which will enable the display of pre-operative tractography on intraoperative anatomical images to guide the surgeon during the resection. Additional validation using visual-evoked potentials recorded from intracranial electrodes (where available) is being studied.

2.107

FOCAL BRAIN ABNORMALITIES IN PATIENTS WITH EPILEPSY WITH ABSENCE SEIZURES: EVIDENCE FROM HIGH-RESOLUTION T1-WEIGHTED AND DIFFUSION TENSOR MR IMAGES

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Rationale: The proposed new classification of the ILAE believes that "generalized" crises exhibit focal onset with rapid propagation, and absence seizures with SWD present generally greater amplitude in the midline of the frontal region. The aim of this study is to evaluate the cortical thickness and white matter (WM) integrity on high-resolution T1-weighted and diffusion tensor (DTI) MR images in patients with

epilepsy with absence seizures and generalized spike-wave complexes discharge (SWD).

Methods: We studied 19 patients (11 female, 24.6 + - 12.1 years) with electro-clinical diagnosis of epilepsy with absence seizures associated with generalized SWD of 3 to 4 Hz and 19 healthy controls matched by sex and age. All patients underwent MRI (1.5 T) with advanced sequences (high-resolution 3D isotropic T1-WI and DTI). The assessment of cortical thickness was performed semi-automatically through the sorftware FreeSurfer. The study of the integrity of the WM (DTI) was performed with TBSS (tract-based spatial statistics), which is part of the FSL.

Results: Patients with absence seizures showed areas of significant reduction of cortical thickness at the right pre-central gyrus (area 4) and precuneus (area 7), and left transverse temporal gyrus (areas 41 and 42). Furthermore, we observed increased cortical thickness in the rostral portion of the left middle frontal gyrus (area 46). A voxel-based analysis of fractional anisotropy maps showed a significant reduction in the right frontal WM and anterior portions of the corpus callosum of patients with CA.

Conclusions: Our results in humans with absence seizures and SWD show changes in the corpus callosum and frontal WM, as well as at the frontal, parietal and temporal cortical regions, supporting the hypothesis of focal network participation in patients with absence seizures and generalized SWD.

2.108

HIPPOCAMPAL VOLUME AS A PREDICTOR OF VERBAL MEMORY DECLINE AFTER LEFT ANTERIOR TEMPORAL LOBECTOMY

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Rationale: Verbal memory decline is frequent after left anterior temporal lobectomy (L-ATL). We showed recently that language lateralization is more predictive of verbal memory decline than Wada memory asymmetry or hippocampal fMRI activation asymmetry (Binder et al., 2008; 2010). Here we assess whether hippocampal volume asymmetry contributes independent predictive value beyond fMRI language lateralization alone.

Hypothesis:

Larger left hippocampal volume and smaller right-left hippocampal asymmetry will be associated with more severe verbal memory decline following L-ATL.

Methods: Participants:

Participants were 53 left temporal lobe epilepsy patients treated with L-ATL. All patients underwent preoperative fMRI using a Semantic Decision - Tone Decision contrast to measure language lateralization (Binder et al., 2008). All patients had preoperative and 6-month postoperative neuropsychological testing, including the 6-trial Selective Reminding Test (SRT), a standardized measure of verbal episodic memory encoding.

Volumetric Measures:

FreeSurfer software was used to create automated parcellations of the hippocampus from high-resolution T1-weighted preoperative structural MRI scans (Pardoe et al., 2009; Shen et al., 2010). A hippocampal asymmetry index was calculated using the formula (right-left)/(right+left), where left and right represent the left and right hippocampal volumes.

Results: Average hippocampal volume was smaller on the left than the right (paired t-test, $p < .00001$), suggesting that the parcellation method is sensitive to hippocampal structural pathology. Both left hippocampal volume ($r = -.267$, $p < .05$) and hippocampal asymmetry ($r = .252$, $p < .05$) were modestly predictive of post-operative verbal memory change on the SRT, with larger left hippocampal volume and smaller asymmetry values correlating with worse postoperative memory outcomes. The fMRI language lateralization index was more strongly correlated with memory outcome ($r = .440$, $p < .001$). Neither left hippocampal volume or hippocampal asymmetry provided additional predictive value when included with fMRI language lateralization in a multivariate regression model.

Conclusions: Preoperative hippocampal volume measures are sensitive to unilateral hippocampal pathology but are only modestly predictive of postoperative verbal memory outcomes. Verbal memory outcome is strongly correlated with language lateralization, supporting recent claims that lateralization of material-specific verbal memory functions is more closely tied to language lateralization than to hippocampal pathology.

2.109

MRI-BASED CORTICAL THICKNESS ANALYSIS IN TEMPORAL LOBE EPILEPSY: REPRODUCIBILITY AND RELATION TO SURGICAL OUTCOME

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Rationale: To assess the reproducibility of neocortical atrophy and its clinical significance across the spectrum of temporal lobe epilepsy (TLE), in particular with respect to post-surgical outcome.

Methods: MRI-based cortical thickness measurements were obtained in 105 patients. 58 had hippocampal atrophy on MR-volumetry (TLE-HA) and 47 had normal hippocampal volumes (TLE-NV). Twenty-seven patients had repeated scans with a mean interval of 28 months. Patients were compared to 48 age-and sex-matched healthy controls. We used linear models to assess cortical thinning and the effect of seizure control after surgery. Reproducibility of finding cortical atrophy was statistically evaluated using bootstrap simulations.

Results: Cross-sectional and longitudinal analyses revealed highly similar topology and rates of neocortical thinning in both TLE groups, predominantly in fronto-central, temporal and cingulate regions. Bootstrap methods showed that at least 20 subjects per group were necessary to reliably observe these patterns of atrophy in TLE (Figure 1). Moreover, power analysis showed that even with sample sizes of 80 subjects per group, differences in thickness between TLE-HA and TLE-NV would be marginal. With respect to post-surgical outcome, we found an association between residual seizures and atrophy in temporopolar and insular cortices in TLE-HA, and in the posterior quadrant in TLE-NV (Figure 2).

Conclusions: We demonstrated with a high degree of confidence that static and dynamic effects of epilepsy impact similarly the neocortex of

patients with TLE-HA and TLE-NV. On the contrary, areas predicting unfavorable post-surgical outcome were distinct, suggesting different configurations of epileptogenic networks in these two groups.

IMAGE: images/905228_A.jpg

IMAGE: images/905228_B.jpg

2.110

TRACT-BASED SPATIAL STATISTICS IN IDIOPATHIC GENERALIZED EPILEPSIES

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Rationale: The thalamo-cortical network is impaired in patients with idiopathic generalized epilepsies (IGEs). Investigations using quantitative neuroimaging were able to depict focal abnormalities in these patients. Diffusion tensor imaging (DTI) is a technique which is able to detect white matter abnormalities. The findings on DTI probably reflects axonal integrity. From previous works we hypothesized that in patients with IGEs the abnormalities are not restricted to the thalamo-cortical network but may be related to white matter changes in other locations allowing the spreading of the epileptiform discharge.

Methods: 14 patients with IGEs (8 women, mean age 28 ± 8) and 22 controls (13 women, mean age 30 ± 10) were investigated. All Individuals were submitted to a 3T MRI scanner. DTI images were acquired using echoplanar imaging sequence with 34 diffusion directions. Images were processed and analyzed using MRIcroN and FSL softwares. Initially images were converted into Neuroimaging Informatics Technology Initiative (NIfTI) format. Gradient directions and b-values were extracted. Images were then corrected for eddy currents and the fractional anisotropy (FA) maps were calculated. Voxelwise statistical analysis was carried out using TBSS (Tract-Based Spatial Statistics), part of FSL software. FA maps were aligned into a standard space using nonlinear registration. Next, a mean FA image was created and thinned to create a mean FA skeleton which represents the centres of all tracts common to the patients and controls. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics (Figure A). Statistical analysis was conducted using t-test corrected for multiple comparisons.

Results: Comparison between patients and controls revealed areas of increased FA in IGE group localized mainly at the corpus callosum (data of the maximum voxel) two-sample $t(34) = 5.5$, $p < 0.001$ (MNI coordinates, x= -15mm,y= -43mm, z= 16mm), ventral mesencephalum $t(34) = 6.3$, $p < 0.001$ (x= 12, y= -17, z= -16) and at the anterior limb of the internal capsule $t(34) = 4$, $p < 0.001$ (x= -15, y= 10, z= 6). Figure B depicts the results above reported. There were no areas of reduced FA.

Conclusions: Structural abnormalities were disclosed in the white matter of patients with IGE. Interestingly, in opposition to the literature, FA was increased in the patients. Increased diffusion may facilitate several mechanisms related with the seizures: the corpus callosum contribute to high interhemispheric synchronization; the anterior limb of the internal capsule is part of the thalamo-cortical circuitry which is involved in the maintenance of the generalized discharges; the mesencephalum have an important role in generalized tonic-clonic seizures which were present in all patients investigated in here. Therefore, our findings probably are drawing the whole system involved in IGE pathogenesis.

IMAGE: images/905665_A.jpg

Figure: Results of the Tract Based Spatial Statistics (TBSS) analysis of idiopathic generalized epilepsies (IGE) patients compared to controls. A- Mean FA skeleton (green) overlaid with the mean FA maps of patients and controls. B- Results of the TBSS comparisons showing areas of increased FA localized mainly at the anterior limb of the internal capsule (top row), ventral mesencephalum (middle row) and corpus callosum (bottom row). The results are color coded according to the p-value as demonstrated in the inferior portion of the figure. The findings were superimposed with a FA template. Images are displayed in sagital, axial and coronal slices. Inset shows a zoom in the region of the maximum voxel.

2.111

STRUCTURAL CHANGES IN A FAMILY WITH AUTOSOMAL DOMINANT PARTIAL EPILEPSY WITH AUDITORY FEATURES AND LGI1 MUTATION

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Rationale: Autosomal dominant partial epilepsy with auditory features (ADPEAF) is a benign form of epilepsy associated with mutations in LGI1, and brain magnetic resonance imaging (MRI) usually normal or with minor abnormalities. The objective of this study was to identify areas with abnormal volume and cortical thickness in individuals of the same family with ADPEAF and mutation in LGI1.

Methods: We performed volumetric and cortical thickness analysis in 15 subjects (7 men) with point mutation in LGI1. Ten individuals had normal MRI on visual analyses, and five had enlargement of the left temporal lobe. Ten patients had clinical diagnosis of ADPEAF and the others were asymptomatic carriers of LGI1 mutation. T1-volumetric images (1mm) were obtained in a 2T MRI. Optimized voxel based-morphometry (VBM) with modulation was performed for volume investigation. Images were pre-processed with the program MRIcro® and the software SPM8/DARTEL was used in a Matlab7.5 platform. For this analysis, eighty-five healthy subjects were included for statistical comparison (t-test) in order to identify possible areas of growth or atrophy of gray (GM) and white (WM) matter (minimum of 30 voxels, $p < 0.05$, $T > 4.84$). Cortical thickness analysis was performed with Freesurfer®, with 20 healthy subjects as control group (t-test, FDR, $p < 0.05$, $T > 2.5$).

Results: Individuals with mutation in LGI1 showed areas of GM atrophy in frontal lobes, more significant in left pre-central gyri, and WM atrophy in fronto-temporal regions and cerebellum, more significant in left temporal lobe and right cerebellum (Figure 1). There were no significant areas of GM or WM volume increase in the group of individuals with mutation in LGI. Surface analysis demonstrated reduction of cortical thickness in the transition of left pre-central and post-central region and increased cortical thickness in right posterior temporal lobe and parietal lobe (Figure 2).

Conclusions: In agreement with previous studies showing minor imaging abnormalities predominantly in the left hemisphere in ADPEAF, we found areas of reduced GM and WM concentration mainly in left frontal and left temporal lobes, respectively, and reduced cortical thickness in the transition of left pre- and post-central areas. Right hemisphere abnormalities had not been previously described in

ADPEAF, and we also found increased cortical thickness in right posterior temporal and parietal regions in these individuals.

IMAGE: images/907569_A.jpg

IMAGE: images/907569_B.jpg

2.112

INVERSE RELATIONSHIP BETWEEN STRUCTURAL VOLUME AND HEMISPHERIC CONNECTIVITY STRENGTH IN TEMPORAL LOBE EPILEPSY PATIENTS WITH HIPPOCAMPAL SCLEROSIS

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Rationale: Temporal lobe epilepsy patients (TLE) with hippocampal sclerosis (HS) have reduced hippocampal volume in the diseased hemisphere. The atrophic mesial temporal structures produce excessive excitatory outputs that result in seizures. To understand how white matter connectivity relates to the disparity between volume and neural output, we used probabilistic and deterministic diffusion tensor tractography to quantify connectivity of the sclerotic and non-sclerotic hippocampus of TLE patients.

Methods: Ten TLE patients (2 left, 8 right hemisphere HS) were imaged at 3 tesla (Philips Intera). A T1-weighted MRI and diffusion images (32 directions) were obtained. Automated anatomical parcellation (Freesurfer v4.5.0) of the T1 MRI was used to segment the diseased hippocampus (Dhipp) and non-diseased hippocampus (NDhipp) into separate binary image masks, which were used as seed regions for tract generation using both deterministic (DTI Query v1.1) and probabilistic (FSL v4.1.4) methods. For each patient, an index of inter-hemispheric hippocampal volume difference was computed as: [(NDhipp_vol-Dhipp_vol)/(NDhipp_vol+Dhipp_vol)]. Indices of inter-hemispheric hippocampal connectivity density differences based on numbers of tracts were computed as: [(NDhipp_ntracts-Dhipp_ntracts)/(NDhipp_ntracts+Dhipp_ntracts)]. Indices of inter-hemispheric hippocampal connectivity strength differences based on mean fractional anisotropy (FA) for voxels representing the tracts were computed as: [(NDhipp_fa-Dhipp_fa)/(NDhipp_fa+Dhipp_fa)].

Results: Hippocampus volume in the diseased hemisphere was on average 21% smaller (Dhipp_vol=3146 mm3 vs. NDhipp_vol=3972 mm3, $p<0.008$). A strong positive linear relationship was found between the inter-hemispheric hippocampal volume index and the connectivity density (# tracts) index (Figure 1, $r=0.71$, $p=0.02$ for deterministic and $r=0.98$, $p<0.0001$ for probabilistic). A negative relationship was found between the inter-hemispheric hippocampal volume index and the connectivity strength (mean FA) index (Figure 2, $r=-0.72$, $p=0.02$ for deterministic and $r=-0.74$, $p=0.01$ for probabilistic). The deterministic and probabilistic methods produced a pattern of very similar results ($r=0.75$, $p=0.01$ for density and $r=0.83$, $p=0.003$ for strength).

Conclusions: Automated anatomical parcellation estimated reduced hippocampal volumes accompanying HS. Volume reduction corresponded to fewer white matter tracts connecting the sclerotic hippocampus to the rest of the brain. Importantly, however, the decrease in tract density did not correspond to a reduction in connectivity strength, as measured by mean FA in voxels representing the tracts. In fact, we found the opposite relationship, with mean FA tending to be higher in tracts connecting the sclerotic compared to the non-sclerotic hippocampus. Very similar results were obtained using deterministic and probabilistic methods. We conclude that morphological differences in hippocampus of TLE patients with HS correspond to distinct differences in white matter connectivity density and strength.

IMAGE: images/907021_A.jpg

Relationship between hippocampal volume (x-axis) and connectivity density (y-axis) shows that as the volume of the non-diseased hippocampus increases in proportion to the sclerotic hippocampus, so does the number of white matter tracts. This relationship was significant ($p<0.05$) for both the deterministic and probabilistic analyses.

IMAGE: images/907021_B.jpg

Relationship between hippocampal volume (x-axis) and connectivity strength (y-axis) shows that as the volume of the sclerotic hippocampus decreases in proportion to the non-diseased hippocampus, the average fractional anisotropy of the tracts increases. This relationship was significant ($p<0.05$) for both the deterministic and probabilistic analyses.

2.113

THREE-DIMENSIONAL ATROPHY PATTERNS OF THE THALAMUS IN RECENT-ONSET JUVENILE MYOCLONIC EPILEPSY

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Rationale: The thalamus plays an important role in the modulation and propagation of seizure activity. Recent neuroimaging studies have found reduced thalamus volume in juvenile myoclonic epilepsy (JME). However, the spatial pattern of this atrophy has not been reported and the goal of the current study is to characterize the distribution of thalamic atrophy in recent-onset JME. Using three-dimensional shape analysis, the study aims to test two alternative hypotheses: 1) If the overall pattern of volume reduction in JME is nonspecific, then the distribution of thalamic atrophy should be spread throughout the structure. 2) If thalamic atrophy patterns reflect disruption of specific fronto-thalamic-striatal circuits, then atrophy should be localized to specific regions of the thalamus.

Methods: T1 weighted SPGR images were obtained on a 1.5 Telsa GE Sigma scanner (TR 24 ms, TE 5 ms, slice thickness 1.5 mm) in 21 individuals with recent-onset JME (age = 15.8 +/- 3.0 years; epilepsy duration = 8.5 +/- 3.7 months) and 54 healthy controls (HC, age = 13.3 +/- 3 years). Automated segmentation of the thalamus was performed using FIRST (part of FSL, http://www.fmrib.ox.ac.uk/fsl), which is a model-based segmentation tool that searches through linear combinations of shape modes of variation for the most likely shape, based on T1 image intensity. The automated segmentation process produces binarized masks of each subject's thalamus. Total thalamus volumes from each subject were calculated from these masks and then normalized to total intracranial volume (ICV). Second, the automated segmentation also generates a deformable mesh of vertices composed of a set of triangles. The relative position of each corresponding vertex is then compared between JME subjects and healthy controls in order to determine the specific regions of atrophy. Thalamus three-dimensional shape analysis was carried out using F-statistics and multiple comparisons were corrected with false discovery rate.

Results: Thalamus volume was analyzed by ANCOVA (ICV as covariate). There was a significant difference between groups (F = 8.616, p = 0.005) with the JME group exhibiting significantly smaller thalamic volume (mean = 15027.4 cm3, sd= 1641.2) compared to the controls (mean= 15795.2 cm3, sd= 1291.2). Three-dimensional shape analyses (see figure)showed the thalamus to be affected bilaterally in the regions of the anterior nuclei, mediodorsal nuclei, and pulvinar. Unilateral effects were observed in the right ventrolateral and ventroanterior nuclei.

Conclusions: This study demonstrates that thalamic atrophy in JME is selective in nature, affecting the anterior nuclei, mediodorsal nuclei, and pulvinar bilaterally, with unilateral effects in the right ventrolateral and ventroanterior nuclei. Disturbances in thalamic circuitry are evident in this group of JME patients early in the course of their epilepsy. The specific neurobehavioral consequences of this disrupted circuitry remain to be determined. Supported by NIH 2RO1-44351

IMAGE: images/906028_A.jpg

Thalamic atrophy patterns in recent onset JME

2.114

VOXEL-BASED MORPHOMETRY AND COGNITIVE ABNORMALITY IN BENIGN CHILDHOOD EPILEPSY WITH CENTROTEMPORAL SPIKES

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Rationale: Benign childhood epilepsy with centrotemporal spikes (BCECTS) is a localization-related, idiopathic epilepsy syndrome with benign evolution. Recent studies, however, have reported a higher incidence of neuropsychologic abnormalities including learning and behavioral dysfunctions in BCECTS although their neuroanatomical basis is not fully understood yet. The purpose of this study is to investigate the relationship between neuropsychological functions and structural changes of BCECTS.

Methods: Fifteen children with benign childhood epilepsy with centrotemporal spikes (BCECTS) and sixteen healthy control subjects aged 6 to 17 were enrolled for this study (mean 11.66 ± 3.18 year-old). All subjects were assessed by the Korean version Weschsler Intelligence Scale for Children (K-WISC III), frontal executive function test including Stroop and Trail-making test (TMT). Voxel-based morphometric (VBM) analysis was performed using SPM2 running in MATLAB 7.0. Images for volumetries were segmented into probabilistic maps of gray matter, white matter, and CSF with intensity nonuniformity. For statistical analysis, one-way ANOVA and Pearson's correlation coefficient were used.

Results: Patients with BCECTS performed significantly worse than controls in several domains of the neuropsychological test: 105.09 ± 16.12 vs. 112.67 ± 12.62 for performance IQ, 101.09 ± 8.68 vs. 114.00 ± 13.63 for perceptual organization, 105.00 ± 20.10 vs. 122.50±10.07 for attention, 87.36 ± 10.28 vs. 105.50 ± 16.90 for processing speed. Stroop and TMT showed longer response time and more frequent errors in patient group ($p<0.001$). VBM results revealed regional differences between BCECTS and control groups: most prominently, grey matter density of the bilateral prefrontal lobes (middle frontal gyri) decreased in BCECTS group compared with the control group ($p<0.001$). VBM analysis also demonstrated that TMT response time showed negative correlation with bilateral prefrontal (superior frontal gyri) grey matter densities in BCECTS group.

Conclusions: Compared with controls, children with BCECTS exhibit a pattern of mild diffuse cognitive impairments, as well as significantly poor frontal executive functions. VBM and volumetric analysis in this study shows that BCECTS induced regional changes, which are possibly associated with altered brain functions in those patients. BCECTS might lead to neuroanatomical alterations in patients' brains, which consequently affect their cognitive functions, especially in prefrontal and frontal regions.

2.115

EFFECT OF FOCAL VERSUS GENERALIZED EPILEPSY ON THE DTI OF CORPUS CALLOSUM FOR PATIENTS WITH NORMAL MRI

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Rationale: The role of large white matter bundles in generalized and focal seizures is still unknown. Recently, in an animal seizure model, it was demonstrated that diffusion tensor imaging (DTI) can detect localized decreases in fractional anisotropy (FA) in the anterior corpus callosum (CC) for adult epileptic rats compared to control rats (e.g. Chahboune et al). We investigated whether this observation holds in the case of pediatric patients with non-lesional focal and generalized epilepsies. Specifically, we tested the hypothesis that generalized epilepsy would degrade the functional integrity of CC than focal epilepsy would.

Methods: DTI data from 17 pediatric and young adult epilepsy patients aged 2- 27 years (6 with generalized and 11 age-matched with focal epilepsy) with normal MRI (according to standard radiological inspection) were collected during their routine presurgical evaluations. Then DTI-derived metrics of FA were calculated for the midsagittal CC, which is divided into segments for each patient as described by Witelson (e.g. Witelson et al). After that, comparison of those metrics between generalized versus focal epilepsy groups were carried out for the CC segments.

Results: The FA values for five segments of the CC (ranging from the genu to the splenium) were submitted to a 2(epilepsy groups) by 5 (CC segments) ANOVA which resulted in main effects for both factors and no interaction effect. Specifically, the FA values differed significantly ($p<0.001$) for the different segments in both groups, with the middle segments having the lowest values. This finding concurs with and replicates previous findings with normal and multiple sclerosis subjects (e.g. Khader et al). Moreover, the FA values of CC in the generalized epilepsy group were significantly lower ($p.< 0.002$) than those in the focal epilepsy group indicating that generalized epilepsy is more likely to affect the functional integrity of the CC.

Conclusions: This study provides initial evidence that generalized epilepsy affects the functional integrity of CC more than focal epilepsy in pediatric and young adult patients. Further study will clarify the pathophysiology of this phenomenon and whether the same effect can be observed for older patients.

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2.116

POSTOPERATIVE CHANGES IN FIBER TRACT INTEGRITY AND VISUAL FIELDS AFTER ANTERIOR TEMPORAL LOBECTOMY

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Rationale: To investigate postoperative changes in fiber tract integrity in patients with temporal lobe epilepsy (TLE) following anterior temporal lobectomy (ATL), and to determine whether postoperative changes are (1) stable vs progressive and (2) related to visual field defects.

Methods: Diffusion tensor imaging (DTI) was obtained in seven TLE patients before, 2-months after, and one-year after ATL. Changes in fractional anisotropy (FA) were evaluated in a whole-brain voxelwise analysis, as well within specific fiber tracts. Repeated measures analysis of variance was performed to examine the time course of FA changes within ipsilateral and contralateral fiber tracts. Quantitative visual field analysis was performed to determine whether decreases in regional FA were related to the extent or location of visual field defects.

Results: Patients showed decreased FA two months post-ATL in ipsilateral fiber tracts transected during surgery (parahippocampal cingulum, uncinate fasciculus, inferior longitudinal fasciculus, and fornix), as well as in fiber tracts not directly transected (inferior fronto-occipital fasciculus and corpus callosum). Additional decreases in FA were not observed from 2-months to one-year post-ATL. Visual field defects in most patients were characterized by incomplete quadrantanopias. However, FA reductions in one patient extended into temporo-occipital cortex and the splenium of the corpus callosum and were associated with a complete hemianopia.

Conclusions: Wallerian degeneration is apparent two-months following unilateral ATLs in ipsilateral fibers directly and indirectly affected during surgery. These changes do not appear to progress over the course of a year, but may correlate with the nature and extent of postoperative visual field defects.

IMAGE: images/900369_A.jpg

Automated probabilistic fiber atlas of white matter tracts for a healthy individual. THAL = anterior thalamic radiations; CC = corpus callosum; CST = corticospinal tract; SLF = superior longitudinal fasciculus; FORX = fornix; ILF = inferior longitudinal fasciculus; PHC = parahippocampal cingulum; UNC = uncinate fasciculus; IFOF = inferior fronto-occipital fasciculus.

IMAGE: images/900369_B.jpg

Mean FA change values for each of the ipsilateral and contralateral fiber tracts. Negative values represent a decrease in FA and positive values represent an increase in FA. Fibers with a significant time x side interaction are denoted with a "*." Fibers with a significant main effect of time are denoted with "+."

2.117

DIFFUSION TENSOR IMAGING (DTI) SHOWS MOTOR FIBERS MAY BE INTIMATELY RELATED TO CORTICAL DYSPLASIA

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Rationale: MRI findings in cortical dysplasia typically include a subcortical 'tail' extending radially from the cortical abnormality, toward the ventricle. The appropriate surgical aggressiveness toward this subcortical extent is unknown, but potential for morbidity higher. The ability to demonstrate descending motor fibers, such as with diffusion tensor imaging (DTI), as either separate, or distinct from, the dysplasia could guide surgical planning.

Methods: Patients with DTI studies as part of the evaluation for surgical treatment of intractable epilepys were reviewed. Those with MRI evidence of cortical dysplasia near suspected motor cortex were reviewed. Descending corticospinal fibers were identified using seed values from motor fMRI studies. The relationship between these fibers and the subcortical extent of the dysplasia were reviewed.

Results: Three patients (all male, ages 3,7, and 9) with lesions in or near motor cortex were identified. Motor areas were identified by functional MRI in all three. Descending motor fibers were identified in all. In one example, the fibers could be seen running through the dysplastic cortex (Figure).

Conclusions: Despite the MRI abnormalities and the potential to interfere with fiber tracking, we demonstrate motor fibers that can run adjacent to, or even through, the deep extent of dysplastic lesions near motor cortex. This has implications for surgical management of such lesions in intractable epilepsy.

IMAGE: images/908370_A.jpg

DTI fibers (blue) tracked from motor functional MRI seed (orange) superimposed on Bo map.

IMAGE: images/908370_B.jpg

Axial Bo image showing motor fibers (blue) overlapping the 'tail' of the dysplasia (white) extending from the obvious cortical lesion.

2.118

BENIGN MESIAL TEMPORAL LOBE EPILEPSY ASSOCIATED WITH ISOLATED AMYGDALA OR AMYGDALA AND HIPPOCAMPAL ENLARGEMENT

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Rationale: Magnetic resonance imaging (MRI) is pivotal in defining the presence of an epileptogenic lesion that may coexist with the site of seizure onset. Refractory temporal lobe epilepsy (TLE) may be associated with several benign mesial temporal lesions like hippocampal sclerosis (HS), low grade gliomas, cortical dysphasia and cavernous malformations. More recently adult onset autoimmune limbic encephalitis has been recognized as a cause of refractory TLE

After prolonged febrile and non-febrile seizures the hippocampus (HC) may become enlarged and hyperintense and later atrophy to HS. Temporal lobe surgery for lesional epilepsy carries a more favorable prognosis than nonlesional epilepsy. Therefore identifying a lesion is crucial for prognosis. We describe a cohort of TLE patients with isolated enlargement of amygdala (AG) or amygdala and HC combined with benign epilepsy prognosis.

Methods: Thirty one (17 female) randomly selected patients with symptomatic mesial lesional TLE had AG or AG and HC enlargement on visual analysis of MRI (T1, T2, FLAIR, Gadolinium contrast, and MR Spectroscopy). Three were excluded (1 had no digital MRI and 2 had other obvious MRI lesions). We assessed interictal and ictal EEG features histopathology in operated cases and outcomes with regard to seizures and MRI changes.

Results: Average age was 47 years (range 20-80), epilepsy duration was 14 years (range <1-43). Twenty patients had isolated AG enlargement and eight had AG+HC enlargement, involving right and left temporal lobes equally. In eight patients who had epilepsy surgery histopathology showed HS in two, AG gliosis in one, cortical dysplasia in one and normal structures in four. On repeat MRI at an average of 11 years (range 1 to 30 years), the enlargement resolved in 6 (4 to normal and 2 to HS), and persisted in 14. Majority of MRI reports included low grade glioma in the differential diagnosis. No patient developed further enlargement or malignant features. Of six patients who had AG MR Spectroscopy five showed increased myoinositol levels. Epileptiform discharges were present in 19/28, all but one ipsilateral to the lesion. The seizure types were complex partial in 19, simple partial in 17 and generalized tonic clonic in 17 subjects. AED treatment continues in 20/28 patients, 17 on monotherapy. Nineteen patients (68%) remain seizure free on average 4 years (range 1-9 years) of follow-up.

Conclusions: Mesial temporal lobe epilepsy associated with AG or AG and HC enlargement without MRI signal change has a favourable outcome clinically and on imaging. None of the patients had clincal or electrographic status epilepticus. Less than 25% had epilepsy surgery and on pathology the resected lesions were either normal or benign with no tumor. More than two thirds achieved sustained seizure freedom. About 1/3 are not on AEDs and more than 75% are on AED monotherapy. The precise aetiology for the enlargement remains undetermined.

2.119

COMPARATIVE ABILITY OF VOLUMETRY, T2-RELAXOMETRY, AND MAGNETIZATION TRANSFER RATIO TO PREOPERATIVE LATERALIZATION OF HIPPOCAMPAL SCLEROSIS

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Rationale: The outcome for temporal lobe epilepsy (TLE) with hippocampal sclerosis (HS) is highly dependent of the correct identification of the unilateral or bilateral sclerotic hippocampus. Although the qualitative MRI analysis for one expert identifies more than 80% of the lesions, quantitative MRI is an important adjuvant for lateralization of the normal MRI TLE patients. Volumetry is one of the most used quantitative MRI (qMRI) techniques but others like relaxometry, and in special magnetization transfer ratio (MTR), are controversial. Our goal is to test the lateralizing ability of MTR, relaxometry and volumetry, both isolated and combined in TLE.

Methods: We used the MRI of 32 patients acquired with a 3 T Achieva X-Series (Philips Medical System, Best, The Netherlands). The patients had surgery indicated after evaluation using standardized protocols previously published, and all of them had HS proved by histology. Eighteen had right HS. The hippocampal segmentation was automated using FreeSurfer package and the high-resolution MPRAGE T1-wheighted 3D volume images. Whole brain maps of MTR and T2-relaxometry were computed and the values related to the hippocampus were extracted. The data was analyzed using a discriminant analysis with cross-validation and the normalized difference between hippocampus was also calculated.

Results: Individually volumetric measurements on T1-weighted 3D dataset provided accurate lateralization in 30 of 32 patients (94%), MTR in 29 (91%), and T2-relaxometry in 28 (87%). Using the three techniques combined the correct lateralization was achieved in 97% of the patients.

Conclusions: Volumetry, MTR and T2-relaxometry are valuable qMRI techniques to improve visual analyses of TLE MRI studies, but the combination of these techniques provides complementary information of hippocampal pathology and represents maximal accuracy for preoperative lateralization.

2.120

FRACTIONAL ANISOTROPY AND MEAN DIFFUSIVITY IN TEMPORAL LOBE EPILEPSY WITH AND WITHOUT MESIAL TEMPORAL SCLEROSIS USING TBSS ANALYSIS

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Rationale: Patients suffering from non-lesional medial temporal lobe epilepsy can be divided into 2 sub-groups: TLE with mesial temporal sclerosis as defined by MRI (TLE-mts) and those with normal appearing MRI on visual inspection (TLE-no). Recent investigations have demonstrated separate patterns of brain structure abnormalities

associated with both forms of TLE, suggesting that TLE-no may not simply be a milder form of TLE-mts but rather represents a distinct different clinical TLE entity. In this study, diffusion tensor imaging (DTI) parameters fractional anisotropy (FA) and mean diffusivity (MD) are used to investigate patterns of white matter alterations associated with both TLE-mts and TLE-no.

Methods: 15 TLE-mts (6 left, 9 right onset), 15 TLE-no (9 left, 6 right onset) and 20 controls subjects were studied on a 4T MRI system and 4 EPI based DTI images (TR/TE = 6s/77ms, nominal resolution 2x2x3 mm, 6 encoding gradients, b=800s/mm) were acquired. After averaging of the 4 sets, eddy-current and geometric distortion correction was performed and FA and MD maps were calculated. The images of right TLE patients were right-left flipped so the ipsilateral hemisphere was on the left in all cases. Original and flipped control subject images were also included in the analysis to account for physiological hemispheric differences. The individual FA maps were non-linearly registered to a standard FA template and the derived transformation matrices were applied to the MD maps. The data was analyzed using tract-based spatial statistics (TBSS), from FSL with non-parametric voxel-wise t-tests. Permutation analysis with threshold-free cluster enhancement (TFCE) was used to correct for multiple comparisons.

Results: Compared with controls, TLE-mts patients showed significantly reduced FA throughout the white matter of both cerebral hemispheres (ipsi > contralateral). A significant cluster of FA reduction in TLE-no was revealed in the anterior corpus callosum. There were no statistically significant clusters where FA values in patients exceeded those of controls. No statistically significant clusters were found in analysis of MD values.

Conclusions: In this study widespread FA reduction, a marker for axonal damage, was demonstrated in TLE-mts, while localized FA reduction was found in TLE-no. In TLE-mts FA reduction was consistent with a previous whole brain analysis study. In TLE-no the FA reduction was confined to the anterior corpus callosum which supports previous work demonstrating structural grey matter damage in the frontal lobes. These results add to the growing literature indicating that brain damage in TLE is widespread not confined to the temporal lobes. The TBSS method did not detect significant MD abnormalities in either TLE group. TBSS has been previously shown to be an optimal method for detecting subtle FA changes; however, analysis is confined to the mean tract skeleton which may not be optimal for MD changes, which may occur in the grey matter.

2.121

WHOLE-BRAIN CORTICAL THICKNESS ANALYSIS IN FOCAL CORTICAL DYSPLASIA REVEALS ACCELERATED AGE-RELATED THINNING

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Rationale: Focal cortical dysplasia (FCD) accounts for up to 25% of patients undergoing resective surgery for medically refractory epilepsy (Sisodiya et al., 2009). Quantitative image analyses have suggested structural changes distant to the primary lesion, however, with the exception of one study (Colliot et al., 2006), previous work has included patients with various of malformations (Sisodiya et al., 1995, Woermann et al., 1999), and a consistent pattern of cortical pathology has not been established. Our purpose was to investigate whole-brain cortical integrity in patients with FCD using MRI-based cortical thickness measurements.

Methods: We studied 30 patients (11 males, 30±10 years) with FCD and drug-resistant epilepsy. Mean duration of epilepsy was 23±10 years. In patients who underwent surgery (18/30), classification (Palmini et al., 2004) of the resected tissue revealed balloon cell FCD in 12 and non-balloon cell FCD in 6. The control group consisted of 42 age- and sex-matched individuals (16 males, 30±9 years). We measured cortical thickness using the CLASP algorithm (Kim et al., 2005) on 1.5 T MRI (3D T1-fast field echo sequence TR=18 ms; TE=10 ms, voxel size=1mm3). Two observers manually segmented the FCD lesions on multi-contrast MRI. FCD lesions were located in the frontal (n=21), parietal (n=5), temporal (n=2) and sylvian regions (n=2). Lesion labels were projected to the cortical surfaces. Thickness data and lesion labels were blurred using a 15mm surface-based smoothing kernel prior to analysis. To assess cortical thickness in extra-lesional tissue, we excluded vertices that fell within the blurred lesion labels. We compared patients to controls using vertex-wise two-tailed t-tests. We also assessed the effects of duration of epilepsy and Palmini subtype using linear models. Vertex-wise significances were corrected using the false discovery rate procedure (Benjamini and Hochberg, 1995).

Results: Vertex-wise group analysis (Fig. 1a) revealed bilateral cortical thinning in FCD patients in frontal lobe regions, including pericentral and opercular cortices. Additional areas were seen in supramarginal and temporo-occipital cortices. There were no regions of increased cortical thickness. In areas of cortical thinning, we found a negative correlation (Fig. 1b) between age and cortical thickness in FCD patients ($t=3.2$, $p<0.01$), but not in controls ($t=0.2$, $p=0.4$). Moreover, the thickness in these regions was negatively correlated with duration of epilepsy ($t=2.3$, $p=0.02$). There was no association between histopathological subtype and pattern of cortical thinning.

Conclusions: Despite the histological heterogeneity and variable anatomical topography of the FCD lesions, our results show areas of cortical thinning common to all patients. Progressive cortical thinning with increasing age and disease duration suggests that extra-lesional atrophy is secondary to the cumulative effect of seizures, advocating for early surgery in these patients. The preponderance of frontal lobe involvement may explain some aspects of the cognitive deficits in FCD (Guerrini and Parrini, 2009).

IMAGE: images/906689_A.jpg

IMAGE: images/906689_B.jpg

2.122

DTI OF THE FORNIX AND FRONTAL WHITE MATTER IN CHILDREN WITH EPILEPSY: ASSOCIATION WITH MEMORY AND EXECUTIVE FUNCTION

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Rationale: The fornix and frontal white matter circuits are major white matter tracts whose structural integrity can be quantified using diffusion tensor imaging (DTI). However, structure-function associations for these tracts have not been mapped in children with epilepsy. In this preliminary study, we hypothesized that the structural integrity of the fornix and frontal white matter tracts (ventral and dorsal

anterior forceps) as measured by DTI would reflect functional integrity of memory and executive circuits, respectively, as measured by neuropsychological tests in children with epilepsy.

Methods: Children with focal epilepsy were recruited through the pediatric neurology program at Alberta Children's Hospital. All underwent magnetic resonance imaging (MRI) with DTI as part of a clinical protocol on a Siemens Avanto 1.5T MRI scanner (45 slices, 6 diffusion gradient directions, b=1000 s/mm2, voxel size 2×2×3 mm3). White matter integrity was measured by fractional anisotropy (FA) and apparent diffusion coefficient (ADC) using DTI Studio (Jiang et al. 2006). Tracts were computed after anatomically guided manual placement of ROIs by seeding voxels with FA greater than 0.25 and angle less than 70 degrees. All children were also administered tests of verbal and visual memory (California Verbal Learning Test, Children's Version; CVLT-C; Faces subtest of the Children's Memory Scale) and a parent-rated executive functioning scale (Behavior Rating Inventory of Executive Function; BRIEF). Analyses consisted of partial correlations between DTI (FA, ADC) and neuropsychological variables (CVLT Total, Faces Delay, BRIEF Global Executive Composite) controlling for age.

Results: Participants were 18 children with focal epilepsy [8 girls, 12 boys; age = 11.4 years (4.6); age at epilepsy onset = 5.1 years (4.7); number of AEDs = 1.9 (0.8); number of prior failed AEDs = 1.7 (1.5); seizure frequency in last month = 8.4 (17.7); IQ = 80.1 (21.2)]. In all, 9, 5 and 4 children had a left-hemisphere, right hemisphere or bilateral focus, respectively. Left fornix ADC was significantly related to verbal memory (ADC, r = -.51, p = .05). There was a non-significant trend for an association between FA and verbal memory (r = .46, p = .08), but no significant associations between DTI measurements of the left fornix and visual memory or executive functioning. Right fornix FA and ADC were not associated with any cognitive domains. Dorsal but not ventral frontal white matter FA was highly related to executive functioning (r = -.66, p = .005). Frontal white matter FA values were associated with verbal memory, but not visual memory. Neither fornix nor frontal white matter FA or ADC were related to any epilepsy severity variables or to laterality of seizure focus.

Conclusions: This preliminary study suggests a specific association between left fornix and verbal memory, and between frontal white matter and executive functioning. The study also indicates that the use of DTI as part of a clinical imaging protocol allows mapping of specific structure-function relationships in children with epilepsy.

2.123

AUTOMATIC DETECTION OF "MRI-NEGATIVE" EPILEPTOGENIC CORTICAL MALFORMATIONS WITH SURFACE-BASED MRI MORPHOMETRY

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Rationale: Magnetic resonance imaging has revolutionized the detection of small structural abnormalities in patients with epilepsy. However, many focal abnormalities remain undetected in routine visual inspection. Here we used morphometric MRI to quantify imaging features related to epileptogenic cortical malformations to detect abnormal cortical thickness and blurred gray-white matter boundaries that went undetected by routine clinical visual inspection.

Methods: Using MRI morphometry at 3T with surface-based spherical averaging techniques that precisely align anatomical structures between individual brains, we compared single patients with known lesions to a large normal control group to detect clusters of abnormal cortical thickness and gray-white matter contrast (GWC). To assess the effects of threshold and smoothing on detection sensitivity and specificity, we systematically varied these parameters with different thresholds and smoothing levels. To establish the effectiveness of the technique, we compared the detected structural abnormalities to resection margins, seizure onset zones based on intracranial EEG and pathological features using post-resection histology.

Results: We report optimal parameters by which cortical thickness and GWC features detected previously occult lesions. We present sensitivity and specificity measures for each threshold and smoothing level to allow for selection of parameters based on clinical need.

Conclusions: This automated approach may be a valuable additional clinical tool to improve the detection of subtle or previously occult malformations and therefore may improve identification of patients with intractable focal epilepsy who may benefit from surgery.

2.124

LONGITUDINAL MRI VOLUME IN TEMPORAL LOBE EPILEPSY

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Rationale: There is an extensive literature indicating widespread cortical and subcortical damage in patients with chronic temporal lobe epilepsy (TLE). Less is known about the extent of progressive atrophy over time. In this study, we use a longitudinal design to compare the 4-year MRI volume changes in TLE and controls. Here, we present findings for cortical lobar regions, hippocampus, parahippocampus, entorhinal cortex, cerebellum, thalamus and ventricle size. These regions have shown reliable findings of volume abnormality in TLE, but there has been very little study of their change in brain volumes over time.

Methods: Structural MRI volumes of 17 TLE patients (mean age = 35.1) and 26 age-matched controls were examined at baseline and at 4-year follow-up. TLE patients had a long duration of chronic epilepsy (mean = 24.2 years). No patients underwent surgery in the test-retest interval. FreeSurfer, an automated program used to reconstruct the cortical surface and subcortical structures of the brain was used to determine volume changes. Percent volume change over the four year interval was calculated for each subject and Cohen's d effect sizes were calculated to compare mean differences between groups. Conventional interpretation of Cohen's d classifies effect size findings as small (.2-.5), medium (.5-.8) and larger (>.8).

Results: A distributed pattern of greater lobar volume loss for the TLE group was found in the right medial temporal region (d = .54), left frontal (d = .41), right parietal (d = .44) and right (d = .48) and left occipital lobes (d = .43). Small effect sizes were also noted in the right (d = .44) and left cerebellar cortex (d =.39), with greater volume loss in the TLE group. Total hippocampus volume (d = .58), parahippocampas volume (d = .41), entorhinal cortex (d = .67) showed small to medium effect size effects for volume loss in the TLE group compared to controls. Group differences in ventricular enlargement also showed moderate to strong effect size differences; third ventricle (d = .80), left lateral ventricle (d =.54), right lateral ventricle (d =.66) and fourth

ventricle (d = .45). The thalamus volume difference between groups did not reach levels considered to be a small effect size (d = .04).

Conclusions: The current study indicates widespread volume loss over a four-year interval in chronic TLE. Small to medium effect size differences were found in a distributed set of cortical regions, hippocampus, parahippocampus, enthorhinal cortex, and cerebellum. The strongest effect size was found for the third ventricle. These findings suggest that brain atrophy in TLE continues to progress even in TLE patients with a long duration of epilepsy. Determining factors associated with individual differences in volume loss would be of considerable value.

2.125

INCREASED CORTICAL FOLDING COMPLEXITY IN TEMPORAL LOBE EPILEPSY

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Rationale: Converging evidence suggests that abnormalities of neocortical and hippocampal development may play a role in the pathogenesis of temporal lobe epilepsy (TLE). As sulco-gyral patterns are thought to be a footprint of cortical development, we set out to quantitatively map folding complexity across the neocortex in TLE. Additionally, we tested whether there was a relationship between cortical complexity and features of hippocampal maldevelopment, commonly referred to as malrotation.

Methods: We acquired high-resolution (1x1x1mm) T1-weighted MRI scans at 1.5T in 43 drug-resistant TLE patients with unilateral hippocampal atrophy (22 left TLE, 21 right TLE, 19 males, mean age: 35+/-11 years), and 40 age- and sex-matched healthy controls (17 males, mean age: 33+/-11 years). We applied the Constrained Laplacian Anatomic Segmentation using Proximity (CLASP) algorithm (1) to generate a model of the inner (white matter) and outer (grey matter) surfaces. Absolute mean curvature was calculated on the mid-surface between the white and grey matter and smoothed at 10 and 30mm Full Width Half Maximum. Group t-statistic maps of absolute mean cortical curvature were generated to test for differences in cortical folding between healthy volunteers and left and right TLE patients, which were adjusted for changes in cortical thickness. In patients, the resulting difference maps were used to assess the relationship between changes in cortical curvature and 3D measures of hippocampal positioning created from manual segmentations as previously described (2). Surgical outcomes were available for 36 patients. At follow-up (4+/-3 years), 25 patients had achieved a Engel Class I outcome, while 11 had a Class II, III or IV outcome.

Results: We found increased folding complexity in the temporo-limbic cortices encompassing parahippocampal, temporopolar, insular, and fronto-opercular regions ($p<0.05$, random field theory corrected). Increased complexity was observed ipsilateral to the seizure focus in patients with LTLE, whereas these changes were bilateral in RTLE patients. In both TLE groups, temporo-limbic complexity increases positively correlated with the degree of hippocampal malrotation (LTLE: R=0.45, p=0.034; RTLE: R=0.55, p=0.008). We found tendencies for increased complexity in bilateral posterior temporal cortices in LTLE and contralateral parahippocampal cortices in RTLE to be predictive of unfavorable seizure outcome after surgery.

Conclusions: The anatomical distribution of increased cortical complexity overlapping with limbic seizure networks in TLE and its association with hippocampal malrotation are strong indicators that neurodevelopmental factors may play a role in the epileptogenic process of TLE.

References:

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2.126

VBM AND CORTICAL ANALYSIS IN FOCAL CORTICAL DYSPLASIA REVEAL AREAS WITH WIDESPREAD GM ABNORMALITIES IN CORTEX AND CEREBELLUM

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Rationale: Frontal lobe epilepsy (FLE) with frontal focal cortical dysplasia (FCD) is associated with refractory seizures and involvement of somatosensitive cortex. High resolution MRI investigations have disclosed focal cortical abnormalities and SPECT studies have revealed ictal activation in contralateral cerebellum (cerebellar diaschisis) in FLE. We aimed to investigated GM abnormalities in both cortex and cerebellum, with 2 different approaches, Voxel Based Morphometry(VBM) and Cortical analysis.

Methods: Statistical analysis was conducted with general linear model (two sample T-test) comparing 11 patients with left FLE and FCD (7women, 34±12years) to 25 controls (15women, 32±13years) . All individuals underwent volumetric (3D) T1 weighted images with 1 mm isotropic voxels in a 3T scanner (PHILIPS) using a spoiled gradient echo sequence. We used SPM8/DARTEL (www.fil.ion.ucl.ac.uk) for VBM analysis, searching for differences in GM concentration; results were displayed with p uncorrected and T-statistics >3 as minimum threshold. We used Freesurfer software (www.surfer.nmr.mgh.harvard.edu)for cortical reconstruction and statistical analysis . Images initially underwent motion correction, removal of non-brain tissue, automated Talairach transformation, intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction, and surface deformation. After that, imaging underwent surface inflation, registration to a spherical atlas, parcellation of the cerebral cortex, and creation of a variety of surface based data with maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three dimensional MRI volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface. T-tests with FDR of 5% were performed searching for differences in cortical thickness, hemispheric volume and sulcal depth; results were displayed with significance of $p<0.05$.

Results: Patients and controls were balanced for both gender (p=1) and age (p=0.74). VBM revealed few areas with significantly reduced GM concentration in ipsilateral parietal and frontal lobes, and more extensive areas in cerebellum (bilaterally) (Figure1). Surface-based

thickness anaylsis revealed areas of abnormalities in left motor area and some other scattered areas. Sulci analysis revealed few areas with reduction in both hemispheres. Reduction in hemispheric volume of patients was identified in both sides, more extensive in left hemisphere (Figure2).

Conclusions: Our preliminary results with few patients with left FCD revealed subtle bilateral GM abnormalities, extending beyond the abnormality seen on visual MRI analysis. VBM showed reduced GM concentration mainly in cerebellum and Freesurfer cortical analysis was superior in detecting cortical abnormalities, mainly in motor areas. These abnormalities may be related to seizure propagation and surgical outcome.

IMAGE: images/907552_A.jpg

IMAGE: images/907552_B.jpg

2.127

NOCIFEROUS CORTEX IN REFRACTORY TEMPORAL LOBE EPILEPSY: MEASURING PREFRONTAL ATROPHY

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Rationale: Medically refractory temporal lobe epilepsy (TLE) is one of the more common forms of epilepsy, and these patients are at high risk for cognitive deficits. Many patients with refractory TLE show deficits in a wide range of cognitive domains, including memory and executive functioning. While the etiology of executive dysfunction in these patients remains uncertain, the nociferous cortex hypothesis posits that hippocampal sclerosis is associated with dysfunction in other areas of the brain, as well as concomitant secondary cognitive deficits. The purpose of this study, the first part of a larger project, was to investigate the nociferous cortex hypothesis, and specifically whether hippocampal sclerosis was associated with decreased prefrontal volume. Based on previous research showing simultaneous, progressive atrophy in sclerotic hippocampi and extratemporal regions (Dabbs, Jones, Seidenberg, & Hermann, 2009; Coan, Appenzeller, & Bonilha, 2009) including the prefrontal cortex (Keller, Baker, Downes, & Roberts, 2009), it was hypothesized that hippocampal volume would be positively correlated with prefrontal volume in patients with medically refractory TLE.

Methods: Data from patients with history of early onset, medically refractory medial TLE and hippocampal sclerosis were analyzed. Selection criteria and sample characteristics have been described elsewhere (e.g., Fuerst, Shah, Shah, & Watson, 2003). MRI-based volumetric measurements of both hippocampi and bilateral prefrontal cortex were performed using a three-dimensional SPGR sequence on a GE 1.5T, Signa 5.4 unit. Volumes of the two hippocampi were correlated with left and right prefrontal volume, after both were normalized by total intracranial volume

Results: Two-tailed Pearson correlation coefficients were calculated between the absolute volume of the two hippocampi and the absolute volume of left and right prefrontal areas. Preliminary analyses showed significant positive correlations among hippocampal and prefrontal volumes. All correlations were significant at p d" .05.

Conclusions: Consistent with previous research, preliminary analyses showed significant correlations among hippocampal and prefrontal volumes in patients with refractory TLE. As hippocampal volume decreased, so did bilateral prefrontal volume. Results provide on-going support for the nociferous cortex hypothesis. Future analyses will examine executive dysfunction in light of prefrontal and hippocampal volumes.

2.128

ASSESSMENT OF MRI ISSUES FOR THE VNS THERAPY SYSTEM AT 3-TESLA

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Rationale: To evaluate magnetic resonance imaging related (MRI-related) heating for the VNS Therapy System at 1.5 and 3 tesla (T) using various device configurations and MRI conditions and to assess device function before and after MRI.

Methods: The VNS Therapy System (pulse generator, Model 102; leads Models 300 and 302; Cyberonics, Inc., Houston, Tex, USA) underwent assessment of MRI related heating at 1.5 and 3 T using different positioning configurations, leads, transmit radiofrequency (RF) coils (body and head), RF power levels, and scans on different body regions. The function of the VNS Therapy System was evaluated before and after scanning.

Results: At 1.5 T using a transmit RF body coil, excessive temperature changes were associated with scans of the C-spine/shoulder (+11.5 degrees C, complete system; +29.5 degrees C, lead without pulse generator). The lowest temperature change occurred for the scan of the L-spine. At 1.5 T using a transmit/receive RF head coil, temperature changes did not exceed +0.2 degrees C under the conditions studied. At 3 T using a transmit RF body coil, the highest temperature change occurred with the scan of the C-spine/shoulder (+14.5 degrees C) with the lead configured with no strain relief loops at the vagus nerve. MRI performed using various conditions at 1.5 and 3 T produced no significant alterations in the function of the VNS Therapy System.

Conclusions: MRI-related heating was characterized for a variety of scenarios, identifying unsafe as well as safe conditions. Device function was unaffected by MRI procedures at 1.5 and 3 T. By following specific

conditions, safety guidelines for the VNS Therapy System may be expanded beyond those currently indicated by the manufacturer.

2.129

ABNORMALITIES IN DIFFUSION TENSOR IMAGING OF THE SUPERIOR LONGITUDINAL FASCICULUS AND CINGULUM IN PEDIATRIC PARTIAL EPILEPSY

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Rationale: Partial epilepsy can produce several types of deficits in neuropsychological functions and attention in children. The fronto-parietal superior longitudinal fasciculus (SLF) and cingulum connections play an important role in modulating attention. Diffusion Tensor Imaging (DTI) abnormalities of these tracts have been documented in patients with attention deficit hyperactivity disorder (ADHD). To our knowledge, DTI studies of the SLF have not been performed in pediatric epilepsy. One DTI study of the cingulum in pediatric epilepsy reported abnormalities in apparent diffusion coefficient (ADC), but no difference in fractional anisotropy (FA). We hypothesized that DTI would reveal abnormalities in the SLF and cingulum in children with partial epilepsy that are not detectable on conventional MR imaging.

Methods: 7 children (3 boys) between the ages of 5 and 17 years with a definitive diagnosis of partial epilepsy underwent MR imaging on a 3T scanner. The mean duration of epilepsy was 2.9 + 2.24 years. 6 had medication-resistant epilepsy and 1 had controlled epilepsy. Children with frontal lobe pathology were excluded. Following clinical imaging, all children underwent a DTI sequence using the following parameters: single-shot echo-planar imaging, TE = 90 ms, TR = 8800 ms, 128 x 64 matrix, FOV of 220 mm, and 3-mm slice thickness. Images were acquired with diffusion weighting in each of 6 different directions, all with b-values of 0, 1000. DTI data was analyzed using DtiStudio, version 3.0.1. The SLF and cingulum were first identified using tractography and then regions of interest were placed in the mid-portion of the tract in each hemisphere by a single observer. ADC and FA data were compared to normal age- and gender-matched controls from a pre-existing DTI normative database obtained using the same sequence and field strength. Mean values for both hemispheres as well as values for individual hemispheres were compared between patients and controls.

Results: Mean SLF FA of patients was 0.365 + 0.045 and for controls was 0.410 + 0.026 (Wilcoxon Signed Rank $p = 0.0034$ by hemisphere, $p = 0.031$ by patient). Mean SLF ADC was 77.7 + 6.8 x 10-5 for patients and 79.0 + 5.1 x 10-5 for controls ($p = 0.22$ by hemisphere, $p = 0.69$ by patient). Mean FA of the cingulum in patients was 0.411 + 0.062 and 0.477 + 0.048 in controls ($p = 0.0061$ by hemisphere, $p = 0.047$ by patient). Mean cingulum ADC in patients was 84.4 + 9.8 x 10-5 and 88.3 + 4.8 x 10-5 in controls ($p = 0.25$ by hemisphere, $p = 0.38$ by patient).

Conclusions: Our findings indicate abnormal water diffusion in the SLF and cingulum of children with partial epilepsy in otherwise normal-appearing white matter regions. These abnormalities likely reflect microstructural white matter changes that potentially could contribute to neuropsychological co-morbidity by diminished integrity of a white matter tract that is important in attention. DTI appears to be a useful tool for identifying white matter pathology in children with partial epilepsy that cannot be depicted on conventional MR imaging.

2.130

CORTICAL THICKNESS AND WHITE MATTER/GRAY MATTER BOUNDARY DELINEATION REVEAL DYSPLASTIC SEIZURE INDUCING CORTEX

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Rationale: Cortical dysplasias often lead to seizure activity and subsequently epilepsy. Dysplastic tissue is characterized by thickened cortex, and blurred gray matter/white matter (GM/WM) delineation due to disruptions in developmental cortical migration. Subtle dysplasias often go unobserved using imaging techniques.

Computational methods of quantifying cortical thickness have been used to characterize gray matter thinning signatures of diseases in many population studies. These measures begin at the WM/GM boundary and measure thickness outward to the GM boundary. Image intensity gradients can also be measured by sampling the image across the WM/GM boundary, assessing the sharpness of the tissue transition. We hypothesized that the addition of these two quantitative techniques can lead to better dysplasia detection.

Methods: Two patients with medically retractable epilepsy underwent MR imaging in a work up towards epilepsy surgery. Dysplastic tissue was not observed. Both patients then underwent invasive monitoring with subdural electrodes and follow up resection. High resolution T1 weighted MR images gathered prior to surgery were processed using freesurfer software to measure cortical thickness, and WM/GM boundary intensity gradients. Intensity gradients were calculated by sampling the T1 weighted image in 0.5mm increments beginning 1mm within the GM/WM boundary to 3mm into GM. The slope was then calculated at each point and projected onto the brain's surface (Figure 1 bottom row). Patient cortical thickness data was then compared to ten control subjects. Special attention was given to regions beneath electrodes exhibiting seizure activity. Electrode location maps (figure 1 top row) were created using post-electrode gathered CT and MRI imaging, processed as previously described(1).

Results: Both patients exhibited regions near electrodes later measuring epileptic activity that had greater cortical thickness then controls, and less sharply defined GM/WM boundary than other cortex. Following invasive monitoring, seizure-inducing cortex was removed resulting in seizure freedom.

Conclusions: The results of this preliminary technique study indicate that subtly defined seizure inducing dysplastic tissue can be detected using computational methods measuring cortical thickness and intensity gradients at the GM/WM boundary. We show two cases where seizure-inducing dysplastic cortex was measurable prior to invasive monitoring. These techniques show promise in epileptic surgical planning.

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IMAGE: images/908315_A.jpg

2.131

INCREASED CROSSING OF CORTICO-STRIATAL CONNECTIONS FOLLOWING RESECTIVE EPILEPSY SURGERY IN CHILDREN: A PROBABILISTIC DTI TRACTOGRAPHIC STUDY

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Rationale: In Krynauw's original description (1950) on hemispherectomy for intractable epilepsy, he stated that the hemiparesis/hemiplegia is much more severe if the basal ganglia were also removed. Our own studies using PET scanning have shown that

following large cortical resections in children with intractable epilepsy, robust functional changes occur in the striatum on the side of resection (Chugani & Jacobs, 1994; Chugani et al., 2008), presumably related to plasticity mechanisms. We have suggested that these metabolic changes may be due to increased cortico-striatal projections from the contralateral hemisphere to the ipsilateral striatum. In the present study, we used diffusion tensor imaging (DTI) and probabilistic tractography to test this hypothesis.

Methods: We analyzed postsurgical DTI scans from 8 children (age: 8 ± 4.3 years) with intractable epilepsy who had undergone left-sided cortical resection (anatomical hemispherectomy: 4; subtotal hemispherectomy: 2; fronto-temporal resection: 2) and compared these scans with those from 14 normal controls (age: 7.6 ± 3.1 years). All 8 patients had normal pre-surgical MRI and FDG PET findings in the right hemisphere and became seizure free after surgery. In each child, regions were manually drawn on the left caudate using the structural MRI and used as a seed region for probabilistic tractography (FSL 4.1, Oxford, UK) applying the 'two crossing fibers per voxel' model and 10,000 samples per seed voxel. The mean connectivity values were calculated for 5 contralateral cortical regions (frontal, parietal, temporal, occipital and insular cortex).

Results: Repeated measures ANOVA showed a significant interaction between the 2 groups and the 5 contralateral cortical regions ($F = 2.8$; $p = 0.05$). More specifically, the mean connectivity values between the left caudate and right frontal cortex (57 +/- 21 vs. 17.8+/-16; $p = 0.1$) and insula (1.5 +/- 0.3 vs. 0.47 +/- 0.28; $p = 0.032$) showed an apparent increase in the postsurgical group compared to controls. Whereas connectivity values between left caudate and right parietal cortex showed a decrease (0.95 +/- 1 vs. 4.3 +/- 1; $p = 0.037$), the occipital (0.44 +/- 0.2 vs. 0.83 +/- 0.16; $p = 0.16$) and temporal cortex (1.3 +/- 0.4 vs. 1.7 +/- 0.33; $p = 0.54$) showed no difference in connectivity between postsurgical and control groups.

Conclusions: The specific increase in fiber connectivity between caudate ipsilateral to the resection and contralateral frontal cortex and insula is consistent with our previous findings of functional changes in striatum following resection and supports the notion that, following large cortical resections, the ipsilateral caudate participates in functional reorganization. However, since preoperative DTI scans were not available in this cohort, we cannot exclude the possibility that these connectivity changes were the consequence of the left-sided lesion itself and were already present prior to surgery. This issue will be further elaborated in future studies.

2.132

DIFFUSION TENSOR IMAGING IN CRYPTOGENIC WEST SYNDROME : TBSS ANALYSIS

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Rationale: Cryptogenic West syndrome (WS) has normal development before the onset, and no structural abnormalities are observed on conventional MRI. However, seizure and psychomotor outcome is very diverse. Diffusion tensor imaging (DTI) is an MRI technique that can provide information about white matter fiber orientation and integrity. We prospectively performed DTI to assess white matter abnormalities in patients with cryptogenic WS. Images were analyzed with tract-based spatial statistics (TBSS).

Methods: We studied 9 consecutive patients with cryptogenic WS. Age at the onset of spasms was from 3 to 10 months. Developmental quotient at 1 year of age was from 53 to 100. DTI was acquired using 3T MRI (3.0T Trio, Siemens) at the onset and 1 year of age, and fractional anisotropy (FA) images are constructed. Images scanned at 1 year of age were used for analysis. FA images in patients were compared with those of 9 controls whose mean age at the scan was 12 months. Statistical analysis of FA images was carried out using TBSS implemented in FSL (The Oxford FMRIB Software Library). TBSS projects all subjects' FA data onto a mean FA tract skeleton, before applying voxelwise cross-subject statistics. Individual FA data were then projected onto the skeleton, and then correction for multiple comparisons was performed. Regions with significant differences were identified with threshold: $p<0.05$.

Results: The patients with cryptogenic WS, as compared to controls, showed clusters of significantly decreased FA. Decreased FA was observed in anterior corpus callosum, bilateral deep white matters, and right temporal lobes. On the other hand, no areas of increased FA were observed in patients.

Conclusions: Decreased FA on TBSS may reflect delayed myelination or micro-structural abnormalities, such as microdysgenesis. TBSS is useful to detect latent white matter abnormalities in cryptogenic WS. Decreased white matter integrity may be correlated with developmental outcome in cryptogenic WS.

2.133

CLINICAL AND RADIOLOGICAL PROFILE OF EPILEPSY PATIENTS WITH SIGNAL CHANGES IN THE CORPUS CALLOSUM

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Rationale: T2 hyperintense signal changes in corpus callosum have previously been described in epilepsy patients. Little is known about the mechanisms producing these changes. It is also unknown whether these signal changes have any particular relationship to epilepsy types, seizure frequency or any antiepileptic medications. We characterized the clinical features of these patients and analyzed the radiological lesion seen on MRI in order to find predictors of their occurrence and reversibility.

Methods: We did a retrospective search of children with epilepsy with MRI signal changes in the corpus callosum between 2004-2010. Presence of tumor or other brain lesions including ADEM, which could produce similar signal change was considered an exclusion criterion. Demographic information, seizure type, seizure frequency and anticonvulsants were then ascertained from the database. Time gap between the last seizure and the MRI was also noted. Lesions were divided based on their orientation, apparent diffusion coefficient (ADC) values and whether there was associated corpus callosum thinning.

MRI signal changes were analyzed sequentially in T1, T2, FLAIR, DWI and contrast. The locations and sizes of the lesion were described and available follow up scans were reviewed.

Results: Twelve children (age range -3 months to 15 years; median- 6 years ; M:F-1:3) met the inclusion criteria. 8 had generalized seizures; 2 had occipital lobe epilepsy; 1 had temporal lobe seizures; 1 had neonatal seizures. The seizure frequency was variable. Four had an explosive and prolonged onset of seizures. In 6 of the 10 patients, a prolonged seizure was observed in the week prior to the MRI. There was no relationship to any particular antiepileptic medications (Phenytoin, Phenobarbital, Carbamazepene, Valproate, Oxcarbazepine Lamotrigine, Levetiracetam & Zonisamide).

The MRI lesion was in the splenium of corpus callosum in 10 of the 12 children and in the genu in the other two. It was usually hypo or isointense on T1 and hyperintense on T2 & FLAIR. There was no contrast enhancement. The ADC value of the lesions at presentation was variable. Eight of the twelve children had follow-up MRI, and four of them had complete resolution of the lesion. The splenial lesions with an oval shape and lack of corpus callosum thinning were the most likely lesions to resolve on follow up imaging.

Conclusions: MRI lesions in the corpus callosum may be associated with both generalized or focal epilepsy. The frequency and duration of the seizures immediately before the MRI may play a role. Lesions are not related to any particular antiepileptic medication and may be reversible in about 50% over time.

2.134

CORTICAL THICKNESS EXTRATEMPORAL IN TEMPORAL LOBE EPILEPSY

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Rationale: The hallmark of mesial temporal sclerosis (MTS) is neuronal loss and gliosis the hippocampus and related structures, but brain atrophy and tissue damage have been described far from temporal lobe. Several studies have reported changes in size and cortical thinning in frontal and parietal regions. Evaluating whole brain cortical changes is important for understanding the mechanism of injury. In this study we used the FreeSurfer package to find cortical thickness differences between patients and normal controls.

Methods: 135 patients with MTS and 105 normal controls were studied with one 1.5 Tesla MRI equipment (Magneton Vision Plus, Siemens, Erlanger, Germany). In addition to a standard epilepsy protocol, one MPRAGE T1-weighted whole brain sequence with isotropic 1mm voxel was acquired for each subject. The images were processed and analyzed using FreeSurfer package version 4.5 and Qdec version 1.2.

Results: We found significant cortex thinning in the temporal lobe mostly in inferior temporal gyrus and entorhinal cortex, in the frontal lobe (lateral orbitofrontal cortex, medial orbitofrontal cortex, middle frontal gyrus and superior frontal gyrus), in the parietal lobe (post-central gyrus), and in the lingual gyrus of the occipital lobe.

Conclusions: These confirm the hypothesis that tissue damage occurs far from temporal lobe in TLE, and the pathological process includes cortical thickness reduction probably related to temporal lobe network.

2.135

FRONTO-TEMPORAL PHENOTYPES IN PEDIATRIC EPILEPSY

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Rationale: Volumetric abnormalities are related to psychopathology, impaired cognition, and linguistic deficits in children with and without epilepsy. However, in pediatric epilepsy these comorbidities are differentially related to epilepsy variables, to each other, and to brain volumes. To begin to delineate the brain/behavior profiles of comorbidities found in pediatric epilepsy, we used cluster analysis to determine if these children have specific fronto-temporal volume combinations compared to healthy children. We then examined if these volume clusters were related to the comorbidity profile of the epilepsy subjects.

Methods: 116 children, 45 with complex partial seizures (CPS), 21 with childhood absence epilepsy (CAE), and 50 healthy children underwent MRI scans at 1.5T. Tissue was segmented and total brain, frontal lobe, frontal parcellations (inferior frontal gyrus (IFG), orbital frontal gyrus (OFG), dorsolateral prefrontal cortex (DLPFC)), and temporal lobe (TEMP) volumes were computed. Parents and medical charts provided epilepsy-related information. Psychiatric interviews, IQ, language and achievement tests, parent and child report questionnaires on behavior problems, depression, and anxiety were administered to all subjects. Agglomerative hierarchical clustering was performed on the basis of Euclidean distances computed from the frontal and temporal gray and white matter volumes for each diagnostic group. The resulting clusters were compared on demographic, seizure, psychopathology, cognitive, linguistic, and achievement variables using MANCOVAs.

Results: For both epilepsy groups, the cluster analysis identified two distinct clusters of similar size. One cluster had lower OFG and DLPFC gray and white matter volumes and higher IFG and TEMP gray and white matter volumes (Low OFG/DLPFC). The other cluster showed higher OFG and DLPFC volumes and lower IFG and TEMP volumes (High OFG/DLPFC). The two clusters were not different on demographic, seizure, and cognitive variables except age (Low OFG/DLPFC: 10.9±2.5 vs. High OFG/DLPFC: 9.0±1.9, $p<.001$). Controlling for age, the Low OBG/DLPFC cluster was associated with significantly more children with a psychiatric diagnosis (61% vs. 37%, $p<.05$), Child Behavior Checklist Total and Social Problems (52% vs. 23%, $p<.02$), suicidal ideation (45% vs. 7%, $p<.02$), language (53% vs. 24%, $p<.01$), and math achievement deficits (18% vs. 3%, $p<.04$) than the High OFG/DLPFC cluster. The controls formed a cluster with higher IFG and OFG volumes and lower DLPFC and TEMP volumes (High OFG/IFG) and another cluster with higher DLPFC and TEMP volumes and lower IFG and OFG volumes (Low OFG/IFG). These clusters did not differ on demographic, psychopathology, cognitive, linguistic, or achievement variables.

Conclusions: These findings suggest that children with epilepsy can be categorized into two distinct phenotypes on the basis of abnormalities in frontotemporal volume. These phenotypes have strong associations with behavioral, cognitive, and linguistic comorbidities and are unrelated to clinical seizure characteristics.

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EXTRAHIPPOCAMPAL CORTICAL THICKNESS CHANGES IN TEMPORAL LOBE EPILEPSY

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Rationale: Hippocampal atrophy has been reliably identified using volumetric techniques coupled with high resolution MRI in patients with drug resistant temporal lobe epilepsy. Although hippocampal atrophy is the most common finding in temporal lobe epilepsy, studies using MRI have also shown abnormalities in the surrounding areas of the medial temporal lobe. A study by Bernasconi et al. (Brain, 2005; 128: 2442-2452) found differences in the depth and angle of the collateral sulcus in patients with temporal lobe epilepsy who had suspected malformations of cortical development. In a previous study from our laboratory, we quantified the abnormalities in these patients by identifying increases in the volume of the collateral sulcus using manual volumetrics. This study aims to further quantify these changes by determining if cortical thickness in the collateral sulcus can differentiate these patients from controls. This may help in the understanding and better identification of epileptogenic areas in patients with temporal lobe epilepsy.

Methods: This study examined 6 patients with unilateral left temporal lobe epilepsy, as determined by long term video-EEG monitoring, and 8 age matched control subjects. Those with left temporal lobe epilepsy were selected based on the properties of the ipsilateral collateral sulcus (i.e. deeper and more vertical than other patients with temporal lobe epilepsy). T1 weighted 3-D SPGR pulse sequence MRI images were acquired in all participants. Bilateral hippocampal volumes were derived by manually tracing consecutive T1 coronal slices and cortical thickness measurements of the collateral sulcus gray matter were acquired using Freesurfer software. Finally, statistical analyses were performed in the Freesurfer module comparing the two groups.

Results: Of the 6 patients with left temporal lobe epilepsy 2 had left hippocampal atrophy, the other 4 patients had normal bilateral hippocampal volumes. The results showed a significant ($p<0.05$) increase in cortical thickness in the area of the left but not right collateral sulcus gray matter.

Conclusions: This study was performed to investigate if an increase in cortical thickness of the collateral sulcus gray matter could identify a unilateral cortical abnormality even without the presence of hippocampal atrophy. The increased cortical thickness in this area may be attributed to abnormal cortical development and may be identified as a target for surgical resection. Identifying extrahippocampal epileptogenic areas is important in determining the appropriate surgical approach to reduce seizure frequency in those with intractable temporal lobe epilepsy.

2.137

MESIAL TEMPORAL SCLEROSIS (MTS) IN CHILDHOOD: IS A MUTATION IN THE SCN1A GENE THE MOST COMMON CAUSE?

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Rationale: SCN1A gene mutations have been associated with multiple epilepsy syndromes, most frequently Severe Myoclonic Epilepsy of Infancy (SMEI) and Generalized Epilepsy with Febrile Seizures Plus (GEFS+), but other epilepsies have also been reported including Temporal Lobe Epilepsy (TLE). Although MRI findings have been evaluated in SMEI and familial cases of GEFS+, MRI has not been previously evaluated in an unrelated cohort of children with SCN1A and epilepsy. We report an ongoing retrospective review of patients with SCN1A gene mutations and epilepsy with specific focus on MRI findings in childhood.

Methods: Review of the clinical and MRI data of all patients with SCN1A gene abnormalities detected between 2005 and 2010 was conducted. All patients included had documented abnormalities in SCN1A gene sequencing analysis.

Results: Thus far, 15 patients with SCN1A gene mutation have been identified including 11 males and 4 females, however, one patient did not have an MRI available for review. All but 2 patients had onset of epilepsy within the first year of life and age at most recent MRI ranged from 10 months to 14 years. Three patients (20%) had evidence of mesial temporal sclerosis (MTS) with one patient having asymmetric bilateral abnormalities. Other MRI findings included 4 normal (26.7%), 3 with non-specific signal abnormalities (20%), 2 with generalized atrophy (13.3%) and 2 with other unrelated abnormalities (Chiari I, possible hemispheric asymmetry). Of the 3 patients with MTS, all had earlier normal MRI's (20 to 43 months prior) and were between 3.5 years and 7 years of age when MTS was observed. Only one of these patients had classic SMEI with alternating prolonged hemiclonic febrile seizures and myoclonic seizures. The other 2 patients had no history of prolonged febrile seizures. One patient had a history of simple febrile seizure, and the other had seizure onset associated with administration of vaccinations however it was unclear whether they were febrile.

Conclusions: Our study is the first to look at a group of children with SCN1A gene mutation and MRI findings regardless of clinical phenotype. The patient group revealed 20% had MTS and most of the patients did not have a history of prolonged febrile seizures. Our study indicates that testing for SCN1A gene mutation should be considered in young children with epilepsy and MTS; however, further prospective studies are needed to determine the relationship between MTS and SCN1A.

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WIDESPREAD CORTICAL THINNING IN CHILDREN WITH FRONTAL LOBE EPILEPSY

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Rationale: Despite the relatively higher rate of frontal lobe epilepsy (FLE) in children, few studies have been conducted in pediatric FLE compared to temporal lobe epilepsy. Our hypothesis was that spread of seizure activity outside the frontal lobe due to cortico-cortical connections resulted in alteration in the cortex beyond the frontal lobe in children with intractable FLE. The aim of this study was to identify regions of reduced cortical thickness, surface area and cortical volume beyond the frontal lobe in children with intractable FLE.

Methods: The study has the approval of the institutional research ethics board. Seventeen children with frontal lobe epilepsy, consisting

of 10 females and 7 males, mean age of 11.7 years, who were being evaluated for epilepsy surgery were recruited. Twelve children had left FLE and five children had right FLE. Twenty-six age-matched healthy controls, consisting of 12 females and 14 males, mean age of 11.5 years, were recruited. Volumetric T1-weighted imaging was performed on both patients and controls. The volumetric T1 images of all patients with right FLE were side-flipped so that the seizure focus was on the left side in all patients. Cortical thickness, surface area and volume were measured using FreeSurfer and compared between patients and controls. Regions that demonstrated significant cortical thinning were regressed against age of seizure onset, duration of epilepsy, seizure frequency and number of medications.

Results: Significant cortical thinning in the hemisphere ipsilateral to the seizure focus included the superior frontal, paracentral, cingulum, precentral, postcentral, supramarginal, inferior parietal and superior temporal gyri and contralateral to the seizure focus included the superior and middle frontal, precentral, supramarginal, superior parietal and superior temporal gyri (pd"0.004 in all regions). Regions that showed reduced cortical surface area and volume were similar to those regions that demonstrated cortical thinning, but were less widespread. Age at seizure onset (p=0.003) and frequency of seizures (p=0.002) predicted cortical thinning of the superior frontal gyrus ipsilateral to seizure focus. Duration of epilepsy was a weaker predictor of cortical thinning in the superior frontal (p=0.026) and inferior parietal (p=0.019) gyri ipsilateral to seizure focus. There was no significant association between the number of medications and cortical thinning in the hemisphere ipsilateral to seizure focus (p>0.01). There were also no significant associations between age at seizure onset, duration of epilepsy, frequency of seizures or number of medications and cortical thinning in the contralateral hemisphere (p>0.01).

Conclusions: Widespread cortical changes in children with intractable FLE suggested that spread of epileptogenic focus could lead to widespread injury to the cortex. The strong association between cortical thinning and age of seizure onset as well as seizure frequency indicates that the developing brain is more prone to seizure-induced injury and that this injury is more pronounced with increasing severity of seizures.

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FRACTIONAL ANISITROPY ANALYSIS ON MAJOR WHITE MATTER FIBERS IN CHILDREN WITH MEDICALLY INTRACTIBLE FOCAL EPILEPSY: A DIFFUSION TENSOR IMAGING STUDY

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Rationale: To investigate the micro-structural pathologic changes involving the major white matter fibers in children with medically intractable focal epilepsy

Methods: Twenty-one children with medically intractable focal epilepsy had both pre-operative Diffusion Tensor Imaging (DTI) and epilepsy surgery at the Alabama Children's Hospital in 2008-2009 (Patient group). Thirteen had surgery in the left hemisphere and 8 in right hemisphere. The mean age at epilepsy surgery was 9.50 ± 4.58 years (1 year 8months - 15 year 8 months). The mean post-operative follow-up duration was 16.0 ± 7.20 months (7-28 months). Fifteen (71.4%) have been seizure-free postoperatively. Ten (50%) had visible lesions on the conventional brain MRI pre-operatively. The most common pathology was focal cortical dysplasia (85.7%). Thirty-six, age-matched, healthy controls were compared (Control group). Control data were obtained from a normal pediatric database, which was collected under Human Brain Project and National Research Resource Center Grants (cmrm.med.jhmi.edu). Data from both patients and controls were transferred to the workstation and processed using DTI studio software (http://lbam.med.jhmi.edu/DTIuser/DTIuser.asp) and maps for fractional anisotropy (FA) were created. Regions of interest (ROIs) were outlined bilaterally on axial slices of the colored FA map, which were confirmed by fiber tractography. The ROIs for the major white matter fibers include the genu and splenium of the corpus callosum (commissural fibers), the posterior limb of the internal capsule (projection fibers, chiefly of the cortico-spinal tract), the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus and the superior longitudinal fasciculus (association fibers). FA was determined in each ROI. Statistical analysis used ANCOVA with age and group as independent variables.

Results: In the patient group, the FA values were significantly lower at the genu and splenium of the corpus callosum, right corticospinal tract, bilateral inferior fronto-occipital fasciculus, left inferior longitudinal fasciculus, bilateral superior longitudinal fasciculus compared to controls (p<0.05) (Figure 1). Decreased FA values were more prominent in the patients who had surgery in the left hemisphere compared to controls (p<0.05) (Figure 2).

Conclusions: Decreased FA values suggest that the pathologic changes extend diffusely to most of major white matter fibers in children with medically intractable focal epilepsy.

IMAGE: images/907266_A.jpg

IMAGE: images/907266_B.jpg

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CORRELATION BETWEEN WATER DIFFUSION ABNORMALITIES AND REGIONAL VOLUME REDUCTION IN TLE PATIENTS WITH UNILATERAL HIPPOCAMPAL SCLEROSIS

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Rationale: The most commonly described pathology in temporal lobe epilepsy (TLE) is hippocampal atrophy. However, there is evidence for more widespread damage in the mesial temporal lobe and the limbic network involving the amygdala, the entorhinal cortex, the fornix and the thalamus. In patients with TLE with hippocampal sclerosis (HS), analysis of diffusion tensor imaging (DTI) data provides some indirect radiologic evidence of microstructural changes. We investigated whether the volume changes in mesial TLE could be correlate with water diffusion abnormalities by means of voxel-based DTI analysis.

Methods: In 12 left and 7 right mesial TLE (mTLE) patients with HS, we performed manual volumetric measurement of amygdala, hippocampus, fornix, thalamus and entorhinal cortex on both sides. Mean diffusivity (MD) and fractional anisotropy (FA) data of each patient were then quantified and analyzed by statistical correlation method using SPM8. In this study, we used voxel-based DTI analysis to detect water diffusion abnormalities correlated with regional volume reduction in mTLE patients with HS.

Results: Increased MD and reduced FA value in the bilateral anterior thalamic nucleus were correlated with the regional volume reduction of left amygdala in left TLE patients ($p<0.001$). Increased MD and reduced FA value in the bilateral inferior frontal lobe and uncus were correlated with the regional volume reduction of left hippocampus, and reduced FA value of left amygdale was correlated with the regional volume reduction of ipsilateral hippocampus in same patients ($p<0.001$). In addition, decreased left thalamic volume had the significant correlation with reduced FA value of the prefrontal gyrus, cingulate gyrus and uncus in left TLE cases ($p<0.001$). But, those were not observed in right TLE patients. There was no significant region correlated between DTI parameters and the regional volume change of EC in both side of TLE patients.

Conclusions: Our results demonstrate that water diffusion abnormalities of bilateral anterior thalamic nucleus is correlated with the left amygdala atrophy, but isn't correlated with the hippocampal atrophy. The finding presented here, namely, that the thalamus can be atrophic even in the absence of hippocampal atrophy, provides further evidence that structural damage in the anterior thalamic nucleus occur dependently from amygdala atrophy without hippocampal atrophy. This could be considered the mechanism of TLE without HS. Furthermore, this provides a possibility that TLE without HS is heterogenous or entity different from TLE with HS.

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LONGITUDINAL MRI OF THE LIMBIC SYSTEM IN MEDICALLY INTRACTABLE TEMPORAL LOBE EPILEPSY

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Rationale: There have been a small number of MRI studies demonstrating atrophy of mesial grey matter (GM) such as hippocampus and amygdala in patients with chronic pharmacoresistant temporal lobe epilepsy (TLE). However, it is unknown if limbic white matter (WM) including fimbria-fornix and cingulum are affected under the influence of long-term recurrent seizures in this case. Our objective was to assess (1) white matter tracts of limbic system using diffusion tensor imaging (DTI), (2) total GM and WM volumes, and (3) change of T2 relaxometry of hippocampi in medically intractable TLE patients scanned 5.5 years apart.

Methods: Four patients with TLE and without mesial temporal sclerosis (3 males, 1 female, age at first scan: 33, 33, 45 and 46 yrs) and two healthy volunteers (both male, 55 and 48 yrs) were scanned twice on the same 1.5T scanner using both CSF-suppressed FLAIR DTI and standard DTI, a multi-echo T2 sequence and MPRAGE with a scan interval of 71, 62, 68 and 65 months for patients and 42 months for both controls. Three patients had independent bitemporal ictal abnormalities while one had unilateral right temporal ictal and interictal EEG abnormalities. Left and right fimbria-fornix (Fx) and parahippocampal cingulum (pCg) were identified separately with DTI tractography in DTIStudio to yield fractional anisotropy (FA) and mean diffusivity (MD). Hippocampal T2 was measured by manual region-of-interest. T1-weighted MPRAGE images were segmented into GM and WM to yield volumes using SPM5. The difference (Ä) of the 2nd scan relative to the 1st and the percentage of change were calculated for each parameter.

Results: DTI demonstrated elevated MD bilaterally in the Fx of all patients over 5.5 years (mean $Ä_{MD}=0.081\times10^{-3}$ mm^2s^{-1}, 8.8%) with no difference in controls (mean $Ä_{MD}=0.014\times10^{-3}$ mm^2s^{-1}, 1.4%) whereas Fx FA reduced similarly for both groups (patients: mean $Ä_{FA}$=-0.026, -5.5%; controls: mean $Ä_{FA}$ =-0.037, -7.3%). Notably, the pCg showed elevated FA bilaterally in all patients (mean $Ä_{FA}$=0.043, 10.7%), but not in controls (mean $Ä_{FA}$=-0.0025, -0.5%). MD was decreased in 5/8 but elevated in 3/8 of pCg in patients while MD was decreased in all controls. Brain segmentation demonstrated greater GM volume loss of 29 cm^3 in patients compared to smaller reduction of 4 cm^3 in controls. WM volume reduced similarly in both groups (patients: -8 cm^3; controls: -6 cm^3). T2 analysis revealed one patient with dramatic increased T2 on bilateral hippocampi and the one patient manifesting unilateral EEG abnormalities with increased T2 on the abnormal side (all $Ä_{T2}$>8 ms). T2 changes in controls were small (mean $Ä_{T2}$=3 ms).

Conclusions: Five year longitudinal imaging of medically intractable TLE patients demonstrates significant grey and white matter changes. In general the observed changes (increased T2 and MD and decreased volume) suggest progressive grey and white matter degeneration secondary to seizures. In contrast, increased FA of the pCg is consistent with enhanced integrity as opposed to degeneration of the structure which suggests plasticity of some white matter tracts in response to seizures.

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WIDESPREAD ALTERATIONS OF WHITE MATTER IN TEMPORAL LOBE EPILEPSY: A STUDY USING DIFFUSION TENSOR IMAGING AND MAGNETIZATION TRANSFER RATIO

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Rationale: The temporal lobe epilepsy (TLE) is associated with hippocampal atrophy. However, the brain damage is not limited to limbic structures. The mechanisms underlying extrahippocampal brain damage in TLE are unknown. Seizures or medicines may lead to neuronal damage, but another possible explanation is deafferentation from loss of hippocampal connections. This study we combined the use of Fracional anisotropy (FA), mean diffusibility (D), parallel diffusibility (D//), perpendicular diffusibility (D¥"), and Magnetization Transfer Ratio (MTR) to localize the regions where occur axonal lesion and demyelization.

Methods: Two different MRI sequences were performed involving 33 patients with unilateral TLE (15 left and 18 right) and 20 healthy controls (age matched): (1) Magnetization transfer and (2) diffusion tensor imaging (DTI). Tract-based spatial statistics (TBSS) was applied to analyze the FA data. After, the regions with alteration were studied with D, D//, D¥" and MTR maps. When compare with controls, the decrease of MTR values and/or increase of D¥" indicate demyelization and decrease of D¥" can indicate axonal lesion.

Results: Both patients with left- as well as right-sided mesial sclerosis exhibited widespread degradation of fractional anisotropy (FA). With D, D//, D¥" and MTR maps analysis we found demyelization evidences in corpus callosum (all the parts), left corticospinal tract, fornix, right Anterior limb of internal capsule (in patients with right-sided mesial sclerosis), Retrolenticular part of internal capsule, corona radiate, Sagittal stratum (include inferior longitidinal fasciculus and inferior fronto-occipital fasciculus), cingulum, fronto-occipital fasciculus and uncinate fasciculus. Evidences of Axonal lesion was found in Anterior limb of internal capsule, Posterior thalamic radiation

(include optic radiation), right Sagittal stratum, cingulum and Uncinate fasciculus left (in in patients with left-sided mesial sclerosis).

Conclusions: DTI and MTR measures demonstrate widespread clusters of abnormal in prominent white matter tracts linking mesial temporal lobe structures with other brain areas. Our results are consistent with the hypothesis that exist demyelization and axonal damage in patients with temporal lobe epilepsy.

2.143

THE IMPORTANCE OF DIFFUSION WEIGHTED MAGNETIC RESONANCE IMAGING AND HIPPOCAMPAL APPARENT DIFFUSION COEFFICIENT VALUES IN THE PRE-SURGICAL EVALUATION OF PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Rationale: Temporal lobe epilepsy (TLE) is the most common form of localization related epilepsy considered for epilepsy surgery. Interictal/ictal EEG and clinical data, with conjuction magnetic resonance imaging (MRI) results predict the localization of the epileptic zone in the patient with TLE. An important goal in the pre-surgical evaluation of patients with medically intractable TLE is to quantify hippocampal pathology bilaterally. The purpose of this study is to determine whether interictal apparent diffusion coefficients (ADC) provide a robust means for detecting hippocampal abnormalities in adult patients with chronic TLE undergoing pre-surgical evaluation.

Methods: We examined contribution of diffusion weighted magnetic resonance imaging (DWI) and ADC values for the lateralization of lesion in twenty-six patients (14 female, 12 male; mean age 29 years) with TLE. Twenty healthy subjects served as controls (5 male, 15 female; mean age 29 years). The diagnosis of TLE was based on semiology, interictal EEG, video EEG monitoring, and conventional MRI. In both groups ADC values which were obtained from hippocampus in coronal plane were compared. Diffusion-weighted spin echo echoplanar images (EPI) were acquired with standard head coil for signal reception. In patient group, ipsilateral and contralateral ADC values to the seizure focus were compared.

Results: We determined focal epileptiform discharges in %84 of patients by EEG, and hippocampal zone abnormality in %73 of patients by DWI. Ipsilateral hippocampal ADC values (100,09 ± 7,15 x 10-5 mm2/sec) which were determined in the basis of EEG lateralization were considerably higher than the contralateral side values (85,58 ± 1,83 x 10-5 mm2/sec) and the same side values of controls ($p<0,001$). There was not a significant difference between the contralateral side ADC values of patients and controls. We could not find bilateral hippocampal abnormality in MRI, whereas DWI showed bilateral changes in %19 of TLE patients. There was no any relationship between ADC values and clinical variables such as sex, duration of epilepsy, frequency of seizures, and history of febrile convulsion/status epilepticus. The results demonstrated a correlation between lateralizing ictal semiology and ADC values (Spearman r = -0,643; p = 0,033).

Conclusions: It is concluded that DWI is an effective method in the lateralization of lesion side in accordance with EEG data in pharmaco-resistant TLE patients. Furthermore, it may illustrate bitemporal abnormalities which can affect the result of epilepsy surgery. Our preliminary data suggest that quantitative diffusion measurements capture partially complementary aspects of hippocampal pathology.

2.144

MU OPIOID RECEPTOR MRNA EXPRESSION, BINDING AND FUNCTIONAL COUPLING TO G-PROTEINS IN HUMAN EPILEPTIC HIPPOCAMPUS

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Rationale: The main goal of the present study was to characterize the mRNA expression, binding and G protein activation mediated by mu opioid receptors (MOR) in epileptic hippocampus of patients with pharmacoresistant temporal lobe epilepsy (TLE).

Methods: Epileptic hippocampal tissue was obtained from patients with intractable mesial TLE history. Epileptic patients had “en block” anterior lobectomy, ipsilateral to the epileptic focus at least 48 h after the last seizure. During the surgical procedure, hippocampal biopsies were collected immediately upon resection and quickly frozen in pulverized dry ice. Hippocampus obtained at autopsy from subjects with no evidence of neurological disease was used as controls. The human hippocampus tissue was used to evaluate MOR and GAPDH mRNA expression, saturation binding and 35S-GTPãS functional assays.

Results: In contrast with autopsy samples, hippocampus obtained from patients with epilepsy demonstrated enhanced MOR mRNA expression (116%). Saturation binding experiments revealed that the Bmax value from the epilepsy group was significantly higher (60%) when compared with autopsy samples, whereas the Kd values from both groups were not statistically different. DAMGO-stimulated 35S-GTPãS binding values from epilepsy group did not demonstrate significant alterations when they were compared with values obtained from autopsies of subjects with similar range of age. However, epileptic group demonstrated high levels of basal binding for the G proteins (136%).

Conclusions: In conclusion, our present data provide strong evidence that the epileptic hippocampus of patients with TLE presents significant alterations in MOR mRNA, binding and signal transduction mechanisms downstream of these receptors. Alternatively, such changes may represent adaptive mechanisms to compensate for other as yet unknown alterations.

2.145

3T BRIAN MRI AND ICTAL FINDINGS OF PATIENTS WITH NON-LESIONAL PARTIAL EPILEPSY REFRACTORY TO MEDICAL TREATMENT

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Rationale: Non-lesional refractory partial epilepsy refers to the presence of a focal ictal onset zone (IZ), normal conventional brain Magnetic Resonance Imaging (BMRI) and lack of therapeutic response to two anti-epileptic medications (AED). This population is considered a good epilepsy surgery candidate, if the ictal zone is well identified. A precise definition of the IZ is critical for surgical planning.

Methods: Our hypothesis is that the IZ, as defined by EEG studies, correlates with abnormalities on a 3T BMRI. We have retrospectively reviewed the medical records of 12 patients that underwent phase I and II comprehensive epilepsy evaluation. In addition, this study has prospectively enrolled 7 patients for a 3T BMRI. Descriptive statistics were performed.

Results: Ninety five percent of the subjects are still receiving at least one AED and 69 % receive two or more AED. Age of onset of seizures is in average 15.9 years of age. All subjects have seizure semiology consistent with a partial ictal onset and the most common symptoms are: staring (64%), repetitive vocalizations (21%), head version (16 %), epigastric discomfort (11%), olfactory hallucinations (11%) and Déjà vu (11%). The average number of seizures per month in the study population was two. Risk factors for epilepsy identified in this cohort are: trauma (32%), genetic predisposition (11%), drug abuse (5%), and stroke (5%). No risk factors were identified in 16% of cases. Lateralization to the left was most commonly seen (42 %) followed by right lateralization (37%) and no lateralization (21 %).Temporal lobe localization occurred in 64% of cases and extra-temporal in 36 %. Neuropsychological assessment revealed an average verbal IQ of 84% (range 55-102),performance IQ 89 % (63-116) and full scale 91% (73-108).Ictal EEG demonstrated the following findings: frontal-temporal(16%),bilateral temporal(27%),left temporal(16%),right temporal(21%),temporal-parietal(5%) and extra-temporal(16%). Interictal discharges correlated with ictal findings in 95% of cases. There was a 100% correlation between the findings on ictal scalp EEG and the post-implant grid. Findings on a Positron Emission Tomography correlated with ictal findings in 59% of cases. Conventional 1.5T-MRI was normal (non-lesional) in 42 % of the cases. However, 58% of cases had a positive MRI correlating with the previously defined IZ. 3T MRI performed in seven cases did not revealed any new findings. Fifteen patients (80%) underwent surgical resection as follows: anterior temporal lobectomy (58.3%), frontal corticectomy (26.5%), temporal-parietal corticectomy (5%) and posterior temporal corticectomy (5%). Pathological examination revealed: subpial gliosis (16%), hippocampal sclerosis (11%), polymicrogyria (5%), and neuronal loss (5%). Most cases (32%) did not demonstrate any abnormality. Seizure outcome revealed that 37% of cases remain seizure-free at six months post-surgery.

Conclusions: Interim data analysis of this ongoing research study reveals that 3T BMRI findings did not show a significant difference when compared with a conventional 1.5T BMRI.

2.146

SUBTLE CORTICAL GYRAL ABNORMALITIES PREDICT FOCAL CORTICAL DYSPLASIA: A REVIEW OF 3 CASES

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Rationale: IDENTIFYING FOCAL NEUROIMAGING ABNORMALITIES MAY LEAD TO FOCAL SURGICAL RESECTIONS AND POSSIBLE CURES FOR MEDICALLY INTRACTABLE AND DISABLING EPILEPSY. THIS ABSTRACT HIGHLIGHTS 3 SUCH CASES AND CHARACTERIZES THE CLINICAL AND NEUROIMAGING FINDINGS IN THESE CASES.

Methods: A RETROSPECTIVE DESCRIPTIVE STUDY OF 3 CASES WITH SUBTLE CORTICAL GYRAL ABNORMALITIES WHO UNDERWENT FOCAL SURGICAL RESECTIONS OF THESE REGIONS AFTER INVASIVE EEG MONITORING OR ELECTROCORTICOGRAPHY WHO WERE CURED OF THEIR EPILEPSY WILL BE PRESENTED.

Results: FOCAL CORTICAL DYSPLASIAS MAY PRESENT WITH SUBTLE GYRAL ABNORMALITIES. THESE CORTICAL GYRAL ABNORMALITIES MAY GUIDE INVASIVE EEG OR ELECTROCORTICOGRAPHY AND MAY DELINEATE SEIZURE ONSETS WITH PRECISION. RESECTION OF THESE AREAS RESULTS IN EXCELLENT SURGICAL OUTCOMES.

Conclusions: SUBTLE CORTICAL GYRAL ABNORMALITIES MAY BE ASSOCIATED WITH INTRACTABLE EPILEPSY AND SEIZURE ONSETS. FOCAL RESECTION AFTER APPROPRIATE EVALUATION IN SELECTED PATIENTS MAY BE CURATIVE.

2.147

PHARMACOKINETIC EVALUATION ON THE INFLUENCE OF ENZYME INDUCING ANTIEPILEPTIC DRUGS ON THE DISPOSITION OF LEVETIRACETAM IN PATIENTS WITH EPILEPSY

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Rationale: Levetiracetam (LEV) is eliminated by renal excretion and, to a lesser extent, by hydrolysis to the inactive metabolite L057. Because the cytochrome P450 enzyme system plays no important role in LEV metabolism, enzyme inducing antiepileptic drugs (AEDs) have been considered not to influence significantly LEV clearance. However, some observations suggest that plasma LEV levels are decreased by enzyme inducing comedication. The aim of the present study was to compare LEV pharmacokinetics in subjects receiving enzyme inducing AEDs (EIAED group) and subjects not receiving enzyme inducers (control group).

Methods: Fifteen subjects receiving chronic treatment with carbamazepine, phenytoin or phenobarbital alone or in combination therapy (EIAED group) and 15 controls matched for age, gender and body weight gave their consent to participate. Subjects receiving enzyme inhibiting comedications such as valproic acid and felbamate, and subjects with altered renal or hepatic function were excluded. Each subjects received after an overnight fast a single oral 1000 mg dose of LEV, and blood and urine samples were collected at regular intervals for up to 24 h. HPLC methods was used to determine LEV concentrations in plasma and LEV and ucb L057 concentrations in urine. Pharmacokinetic parameters were calculated by model independent-analysis and compared between groups by using the Student t-test or Mann-Whitney test, as appropriate.

Results: Compared with controls, subjects in the EIAED group had higher LEV apparent oral clearance (CL/F) values (1.17 ± 0.3 vs 0.93 ± 0.22 mL/min/Kg, means ± SD, $p<0.05$) and shorter LEV half-lives (6.1 ± 1.0 vs 7.3 ± 1.5 h, $p<0.05$). The amount of LEV excreted in urine as unchanged drug and as ucb L057 did not differ significantly between the two groups.

Conclusions: Enzyme inducing AEDs cause a moderate increase in LEV clearance, an effect which is associated with a modest shortening of LEV half-life. The mechanism(s) responsible for this interaction are unclear.

2.148

INFLUENCE OF WIN 55,212-2 MESYLATE, A POTENT NON-SELECTIVE CANNABINOID RECEPTOR AGONIST, ON THE ANTICONVULSANT ACTIVITY OF FOUR CLASSICAL ANTIEPILEPTIC DRUGS AGAINST PENTYLENETETRAZOLE-INDUCED SEIZURES IN MICE

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Rationale: To evaluate interaction of WIN 55,212-2 mesylate (WIN - a potent non-selective cannabinoid receptor agonist) with four classical antiepileptic drugs (AEDs), clonazepam, ethosuximide, phenobarital, and valproate in the mouse pentylenetetrazole-induced seizure model.

Methods: Clonic phase of pentylenetetrazole-induced convulsions was taken as the endpoint for the occurrence of seizure activity. Total brain concentrations of AEDs were measured by immunofluorescence. The experimental procedures were approved by the Local Ethics Committee at the Medical University of Lublin.

Results: In the dose range of 5-15 mg/kg, WIN given intraperitoneally 20 min prior to the convulsive test, did not affect the convulsive threshold to pentylenetetrazole. When administered at 15 mg/kg in combinations with intraperitoneal AEDs, WIN enhanced the protective activity of ethosuximide, phenobarbital, and valproate, reducing their ED50 values against pentylenetetrazole (85 mg/kg subcutaneously) from 148, 13,9, and 137 mg/kg to 104, 8.3, and 85.6 mg/kg, respectively. At lower doses of 5-10 mg/kg, WIN was without effect upon the anticonvulsant action of classical AEDs. Pharmacokinetic estimations revealed that WIN (15 mg/kg) significantly elevated the total brain concentrations of ethosuximide and valproate, by 26 and 50%, respectively.

Conclusions: Out of four combined treatments of WIN with AEDs, three were encouraging. However, only that with phenobarbital was pharmacodynamic in nature.

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2.149

VOLTAGE-DEPENDENT CALCIUM CHANNEL AND NMDA RECEPTOR ANTAGONISTS AUGMENT ANTICONVULSANT EFFECTS OF LITHIUM CHLORIDE ON THE PENTYLENETETRAZOLE-INDUCED CLONIC SEIZURE IN MICE

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Rationale: There is some evidence that lithium could modulate seizure susceptibility in a variety of models of seizures in animals and epileptic patients. However, the underlying mechanisms of action of lithium have not been completely demonstrated. In this study using several calcium channel blockers (CCBs; nifedipine, verapamil, and diltiazem) and N-methyl-D-aspartate (NMDA) receptor antagonists (ketamine and MK-801) the involvement of calcium signaling in the effects of lithium chloride on pentylenetetrazole (PTZ)-induced seizure.

Methods: PTZ-induced clonic seizure threshold was determined by inserting a 30 gauge butterfly needle into the tail vein of male Swiss mice (23-29 g) and the infusion of PTZ (0.5%) at a constant rate of 1 ml/min to unrestrained freely moving animals. Infusion was halted when forelimb clonus followed by full clonus of the body was observed. Minimal dose of PTZ (mg/kg of mice weight) needed to induce clonic seizure was considered as an index of seizure threshold. The one-way or two-way analysis of variance (ANOVA) followed by Newman-Keuls post hoc test was used to analyze the data. $P < 0.05$ was considered the significance level between the groups.

Results: Acute lithium administration (5-100 mg/kg, i.p.) significantly ($P < 0.01$) increased the seizure threshold. CCBs (5-20 mg/kg, i.p.) and NMDA receptor antagonists (0.1-5 mg/kg ketamine and 0.01-0.1 mg/kg, i.p.) also exerted a dose-dependent anticonconvulsant effects on the PTZ-induced seizures. Non-effective doses of CCBs (nifedipine, verapamil, and diltiazem; 5 mg/kg, i.p.) when combined with non-effective dose of lithium (5 mg.kg, i.p.) exerted a significant anticonvulsant effects. Moreover, co-administration of non-effective doses of either MK-801 (0.05 mg/kg, i.p.) or ketamine (5 mg/kg, i.p.) with non-effective dose of lithium (5 mg/kg, i.p.) significantly increased the seizure threshold.

Conclusions: Our findings demonstrated that lithium increased the clonic seizure threshold induced by PTZ in mice and there is an interaction between lithium with either CCBs or NMDA receptor antagonists in this effect, suggesting a role for Calcium signaling in the anticonvulsant effects of lithium in the PTZ model of clonic seizures in mice. Additionally, our data may provide a new insights into the treatment of clonic seizure using low doses of lithium in combination of low doses of either CCBs or NMDA receptor antagonists.

2.150

CROSS-SECTION STUDY OF 389 VETERANS ANALYZING THE EFFECT OF AEDS ON CHOLESTEROL LEVELS AND SIMVASTATIN DOSE UTILIZATION IN CLINICAL PRACTICE

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Rationale: Several studies have shown that certain AEDs affect the metabolism of cholesterol in the liver by interacting with the cytochrome P450 (CYP450) system. In addition, HMG-CoA reductase

inhibitors (statins), one of the major therapies for hypercholesterolemia, are also metabolized in CYP450. Many anti-epileptic drugs (AEDs) induce the metabolism of CYP450, thus creating a potential significant drug interaction. We hypothesize that patients on enzyme inducing AEDs (EIAEDs) would have higher cholesterol, LDL and HDL levels compared to those on non-enzyme inducing AEDs (NEIAEDs). In addition, when comparing EIAEDs with NEIAEDs in patients on statins, we proposed that the EIAED group would have higher dose utilization when compared to patients on NEIAEDs.

Methods: This study is a retrospective analysis of men and women Veteran patients who attend an out-patient seizure clinic at the Audie L Murphy VAMC in San Antonio, TX. The study consisted of two arms: patients on AEDs and patients on AEDs plus simvastatin. Simvastatin was chosen as it is the first line cholesterol lowering agent at the VA. The patients were on at least one AED and simvastatin for 6 months at a steady dose prior to cholesterol levels being examined. Patients taking other classes of cholesterol lowering medications were excluded. Also, patients taking valproate, an inhibitor of 3A4, were excluded. Medication dosing and type were reviewed and cholesterol levels were analyzed. Comparisons in simvastatin dose and cholesterol levels were made between patients taking EIAEDs and NEIAEDs and were analyzed using the standard t test with unequal variance.

Results: The retrospective analysis consisted of 167 consecutive patients who were taking simvastatin (10 mg - 80mg daily) and an AED, and 222 patients taking only an AED. These groups were further divided into patients on at least one EIAED and those on only NEIAEDs. When comparing total cholesterol (TC) and LDL in patients on statin therapy and patients not on statin therapy, the EIAED group had significantly higher levels. Furthermore, in both groups (with statin therapy and without statin therapy), patients on EIAEDs had higher levels of TC and LDL. Finally, the average daily dose of simvastatin was significantly higher ($p<0.05$) in the EIAED group at 45.12 (±2.7) mg compared to 37.87 (±0.35) mg in the NEIAED group.

Conclusions: This retrospective cohort study demonstrates that EIAEDs do have a significant effect on metabolism of cholesterol, leading to higher levels of both TC and LDL. In addition, the higher simvastatin dose utilization in the EIAED group shows that induction of the CYP450 system also affects simvastatin metabolism. In all, EIAEDs not only inherently increase the levels of TC and LDL, but also induce the metabolism of simvastatin, making it less efficacious and thus contributing to higher cholesterol levels. More studies are needed to assess whether the risk for cardiovascular morbidity and mortality is increased in this patient population as a result of choosing a particular class of AED.

Patient Characteristics

IMAGE: tables/906223_T1.jpg

IMAGE: tables/906223_T2.jpg

2.151

DIFFERENCES IN TOLERABILITY AND DISCONTINUATION RATE OF LACOSAMIDE AMONG PATIENTS WITH OR WITHOUT CONCURRENT SODIUM CHANNEL BLOCKING AEDS

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Rationale: Lacosamide (LCM), (R)-2-acetamido-N-benzyl-3-methoxypropionamide, is a functionalized amino acid with a novel anticonvulsant activity. LCM was approved as an adjunctive treatment for partial-onset seizures in patients e" 16 years by the European Commission (August 2008) and in patients e" 17 years by the U.S. Food and Drug Administration (October 2008). LCM has a novel mode of action (MOA) that appears to be different from existing AEDs, namely the selective enhancement of slow inactivation of voltage-gated sodium channels. However, clinicians have noted that LCM is less well tolerated when it is added to other conventional sodium channel blocking AEDs (SCNBs) such as phenytoin, carbamazepine, oxcarbazepine, or lamotrigine when compared to non-sodium channel blocking AEDs (non-SCNBs).

Methods: In order investigate the differences in tolerability of LCM among patients who are already taking SCNBs, we obtained retention data of LCM retrospectively by reviewing clinic records at the Barrow Neurological Institute. The data included patient's age, gender, seizure type, current AEDs, dosage, main reason for discontinuation, and the duration of therapy. To avoid as much bias as possible, only those patients who added LCM after June 3, 2009 and patients were excluded if LCM was started less than six months prior to this study. The patients were then divided into two groups depend on the presence or absence of SCNBs in their concurrent AEDs.

Results: A total of 185 patients were taking LCM since June 3, 2009, and among them, LCM was started 6 months or longer in121 patients as an adjunctive therapy for partial epilepsy. Eighty-eight patients were taking at least one of SCNBs (Group A) and 33 were taking non-SCNBs (Group B). Discontinuation of LCM was seen significantly higher in Group A (27.27%) when compared to Group B (9.09%) in 6 months ($p<0.0015$). The overall discontinuation rate was 20.66% in 6 months after LCM was added. Dizziness was the leading cause of discontinuation (5.79% of 121 patients), and all occurred in Group A (25% of causes for discontinuation in Group A), and none of Group B patients discontinued LCM due to dizziness side effects.

Conclusions: This study supports the notion that LCM is less well tolerated when added to SCNBs compared to non-SCNBs as an adjunctive therapy for partial epilepsy. Even though LCM demonstrates unique MOA of selectively enhancing slow inactivation of voltage-gated sodium channels, there may be some pharmacodynamic interactions with other conventional SCNBs, which may impact tolerability of LCM (especially dizziness). Further large prospective studies are needed to confirm the findings of our study, but at this point, LCM should be increased more cautiously when added to SCNBs.

2.152

PHARMACOKINETICS AND CLINICAL EXPERIENCE OF RUFINAMIDE IN TREATING CHILDREN WITH SEVERE EPILEPSY

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Rationale: Rufinamide (RUF) is a recently approved antiepileptic drug (AED) used mainly in refractory epilepsy in children. The knowledge is limited concerning its pharmacokinetics as well as its efficacy in different types of epilepsy. We retrospectively evaluated the dose-related plasma concentrations and efficacy in the first 39 children treated with RUF in our clinic.

Methods: The cohort of 39 children, 21 boys and 18 girls, had a mean age of 9.7 years. Their epilepsy onset was at a mean of 1.8 years. Generalized epilepsy was found in 28 and partial in 11. The etiology was heterogeneous. All had pharmacoresistant epilepsy. Clinical efficacy was categorized as >50% seizure reduction, 0-50% seizure reduction, no change or worsening. As a measure of RUF apparent oral clearance, we used the RUF dose-to-concentration ratio which was calculated as: total RUF dose/kg body weight / RUF plasma concentration at steady state. The unit used was (L/[kg/day]). The RUF clearance was related to age and comedication.

Results: A >50% seizure reduction was found in 20.5% (8/39) in the study cohort and in 18% (2/11) in those with Lennox-Gastaut syndrome. No correlation was found between age, gender, type of epilepsy or seizures and seizure response. In the study group, the RUF mean dose was 19.8 mg/kg/d (range 10-39) and the mean plasma level was 28 ìmol/L (range 7.2-83). RUF clearance was higher in younger children and the clearance changed significantly in relation to age (p=0.026; regression analysis). Enzyme-inducing AEDs seemed to induce RUF clearance only to a minor degree (6.7%). Children on valproate had a lower RUF clearance than those not on valproate. In younger children (<10 years), RUF clearance was 41% lower if combined with valproate compared to not on valproate.

Conclusions: Rufinamide clearance was affected by age as well as comedication in this cohort of children. The lower the age of the child the higher the RUF clearance. On comedication with valproate, RUF clearance was significantly lower in the group of younger children. Thus, in the clinic, it should be of importance to take into account the age of the child as well as the type of comedication and consider the expected differences in achieved plasma levels of rufinamide.

2.153

AN EVALUATION OF THE EFFECT OF ESLICARBAZEPINE ACETATE ON WEIGHT, GLUCOSE, AND LIPIDS: AN INTEGRATED ANALYSIS OF THREE DOUBLE-BLIND PHASE III CLINICAL STUDIES

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Rationale: Eslicarbazepine acetate (ESL) is a novel voltage-gated sodium channel blocker currently in development for the treatment of partial-onset seizures in adults. To gain an understanding of the nature and risk of changes in weight, glucose, and lipids when using ESL as an adjunctive antiepileptic drug (AED), these metabolic parameters were analyzed in subjects taking ESL compared with placebo as adjunct therapy to 1-3 concomitant AEDs in the pooled data of 3 Phase III studies.

Methods: We studied all (N=1049) subjects who received at least 1 dose of study medication (400 mg, 800 mg, or 1200 mg of ESL or placebo). The incidence of sponsor-defined potentially clinically significant (PCS) and mean change from baseline values were analyzed by treatment group. PCS values were defined as an increase or decrease of 7% for weight; f″40 mg/dL or g″175 mg/dL for glucose; g″3x ULN for AST and ALT; and >300 mg/dL for TC; >160 mg/dL for LDL-C; <30 mg/dL for HDL-C; >2.5 x ULN for TRIG. TEAEs were defined as an event that occurred on or after the date of first dose, or the date of randomization if the date of the first dose was missing.

Results: PCS incidences for each treatment group are summarized in Table 1 below. Mean changes from baseline to end of the double-blind period for each treatment group are shown in Table 2. The incidence of TC related AEs in the ESL treatment groups was similar to placebo.

Conclusions: No consistent pattern of PCS values was observed for weight, glucose, AST, ALT, TC, LDL-C, HDL-C, or TRIG across the treatment groups. No clinically significant mean changes from baseline were observed. The incidence of AEs related to these metabolic parameters was similar between the eslicarbazepine acetate and placebo treatment groups.

Patients with PCS Parameter Values in Integrated Phase III Studies (Safety Population)

IMAGE: tables/904708_T1.jpg

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase, ESL=eslicarbazepine acetate; TC=total cholesterol; LDL-C=low density lipoprotein cholesterol; HDL-C=high density lipoprotein cholesterol; TRIG=triglycerides; N=number (safety population); n=number (laboratory safety population); PCS=potentially clinically significant; QD=once-daily; ULN=upper limit of normal values; [3]%=change from baseline.

[a]Number of subjects in the safety population who were evaluated for potentially clinically significant value.

Note: PCS events were defined by the sponsor.

Note: Subjects are counted at most once in each category.

Mean change from baseline in metabolic parameter by visit for the integrated Phase III studies (Part I 2093-301, 2093-302, and 2093-303; safety population)

IMAGE: tables/904708_T2.jpg

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase, ESL=eslicarbazepine acetate; TC=total cholesterol; LDL-C=low density lipoprotein cholesterol; HDL-C=high density lipoprotein cholesterol; TRIG=triglycerides; N=number (safety population); n=number (laboratory safety population); QD=once-daily; SD=standard deviation; Trt=treatment; Ä=change from baseline.

Note: Baseline is defined as the last visit prior to first dose of study medication with non-missing data for the laboratory parameter of interest.

Note: Subjects with ALT (SGPT) values of '<5 units/L' were analyzed as if the value was 5 U/L (5 units/L).

2.154

RESPONSE TO AED TREATMENT IN A TERTIARY EPILEPSY CENTER IN 2003-09

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Rationale: About 35% of epilepsy patients are pharmacoresistant. Since 1993 12 new AEDs have been introduced. The most recent studies of AED response occurred before widespread use of the second wave of the new AEDs (levetiracetam, oxcarbazepine, zonisamide, pregabalin, lacosamide) (1,2). They suggested that seizure freedom occurs in d"3% of patients who fail to respond to 3 AEDs or are treated

with polytherapy. In the present study, we evaluated the response to AEDs during years 2003-09 in a tertiary epilepsy center.

Methods: The charts of all patients evaluated and treated consecutively between 2003-09 at one tertiary epilepsy center were reviewed for response to AED therapy. Epilepsy was classified using ILAE criteria. AED choice was based on estimate of best fit of AED(s) for each patient, using epilepsy type, AE potential, comorbidity, pharmacokinetics, drug-drug interaction and ease of use as choice determinants. Response was defined as seizure freedom for 12 months.

Results: 583 patients (367 [63%] F, 216 [37%]M) were evaluated. Mean age was 42 years (range 11-89), mean epilepsy duration 17.5 years (range 1-76). 510 (87.48%) patients had localization related epilepsy (LRE), 73 (12.52%) primary generalized epilepsy (PGE).

237/583 (40.7%) became seizure free, including 195/510 (38.2%) LRE patients and 42/73 (57.5%) PGE patients.

62/510 (12.2%) LRE patients responded to the first AED, 48/510 (9.4%) to the second AED, including both mono- and polytherapy, and 30/510 (5.9%) to the third. 10.9% became seizure free with the use of e”4th AED: 27/510 (5.3%) with the fourth, 9 (1.8%) with the fifth, 7 (1.4%) with the sixth, 8 (1.6%) with the seventh, 3 (0.6%) with the eighth, and 1 (0.2%) with the ninth.

9/73 (12.3%) PGE patients responded to the first AED, 10 (13.7%) to the second, and 13 (17.8%) to the third. 15.1% became seizure free with the use of e”4th AED: 4/73 (5.5%) with the fourth, 3 (4.1%) with the fifth, and 0-2 (0-2.7%) with the sixth-eleventh AEDs.

116/510 (22.8%) of LRE patients responded to monotherapy, 79/510 (15.5%) to polytherapy. 31/73 (42.5%) of PGE patients responded to monotherapy, 11/73 (15.1%) to polytherapy.

LRE monotherapy: 38/510 (7.5%) patients responded to LEV, 21 (4.1%) to CBZ, 15 (2.9%) to PHT, 14 (2.8%) to LMT, 12 (2.4%) to VPA, 8 (1.6%) to PB, 3 (0.6%) to GBP and 2 (0.4%) to TPM.

LRE polytherapy: 5/510 (1%) each of LRE patients responded to combinations of LEV+LMT and LEV+TPM, 4/510(0.8%) to VPA+LEV, and 3 (0.6%) each to CBZ+LMT and to TPM+LEV+LMT. Response to other combinations was limited to 1-2 patients.

PGE monotherapy: 15/73 (20.6%) of PGE patients responded to VPA, 8 (11%) to LEV, and 3 (4.1%) to LMT. Response to other AEDs was limited to 1-2 patients.

PGE polytherapy: 11/73 (15.1%) of PGE patients became seizure free on polytherapy, but d”2 patients responded to any one combination.

Conclusions: 10.9% of LRE patients and 15.1 % of PGE patients became seizure free after failing 3 AEDs.

15.5% of LRE and 15.1% of PGE patients achieved seizure freedom on polytherapy. AED response may be greater than previously thought with the use of new AEDs.

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USE OF RETROSPECTIVE DATA AND A STRUCTURED DECISION APPROACH TO CHARACTERIZE DRUG-LEVEL AND PATIENT-LEVEL ANTIEPILEPTIC DRUG RESPONSE FOR THE EPILEPSY PHENOME/GENOME PROJECT

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Rationale: Several previous studies of possible associations between specific genetic variants and variability in antiepileptic drug (AED) response have had conflicting results. This may be due in part to the lack of consistent methods to assess drug response, and the use of dichotomous measures, with no option for an indeterminate response. These problems with classification could have diluted the findings from previous studies. As part of the Epilepsy Phenome/Genome Project (EPGP), a study that will include 1500 sibling pairs with either idiopathic generalized epilepsy (IGE) or non-lesional localization-related epilepsy (LRE), we developed a structured decision approach for classifying AED response on an individual AED drug level, as well as for identifying “drug resistant” patients.

Methods: Expert consensus was used to develop the key nodes for a decision tree approach to characterizing treatment success or failure for individual AED trials. The nodes were duration of therapy (> 3 months, d” 3 months), longest seizure free interval (< 12 months, e” 12 months), fraction of Defined Daily Dose [DDD] achieved (< 50%, e” 50%), number of seizures during titration or maintenance, and occurrence of provoked seizures. AED trials that do not meet the criteria for either success or failure are considered uninformative and will not contribute data to planned genome analyses. Based on response to individual AED trials, patients are characterized either as “pharmacoresistant” (no AED successes and 2 or more AED failures) or “pharmacosensitive” (at least 1 AED success and fewer than 2 AED failures). AED response is assessed by retrospective review of available medical records.

Results: AED response data are available for 1358 individual AED trials in 419 sib-pair participants with IGE or LRE (average of 3 AED trials per participant). Of these AED trials, 373 (28%) were “failures”, 172 (13%) were “successes” and 508 (37%) were “uninformative”. For 18% of the AED trials, key data elements were missing and response could not be determined. Among all 419 participants, 176 (42%) could be classified as either pharmacoresistant or pharmacosensitive. The remaining 243 participants did not meet criteria for either pharmacoresistance or pharmacosensitivity. Among the 176 “classifiable” participants, 59 (34%) were pharmacoresistant and 117 (66%) were pharmacosensitive.

Conclusions: Using a structured approach to the phenotypic characterization of AED response in EPGP sib-pair participants, we are able to use retrospective data to determine treatment success or failure in 40% of 1358 AED trials. We are also able to characterize patient-level response (pharmacoresistant or pharmacosensitive) in 42% of enrolled subjects. These data may contribute meaningful and unambiguous phenotype information for planned genome analyses.

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PHENOBARBITAL-INDUCED APOPTOSIS IN THE NEONATAL RAT BRAIN OCCURS IN A LIMITED COMPARTMENT OF NEURONS

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Rationale: During the period of active synaptogenesis, the immature brain is vulnerable to enhanced neuronal apoptosis (ENA) induced by a variety of drugs. In rodents, this vulnerability is manifest during the first two postnatal weeks in response to alcohol, anesthetics, and certain antiepileptic drugs, such as phenobarbital (PB). In addition, long-term behavioral deficits have been observed following neonatal exposure to these drugs, suggesting that drug-induced ENA may contribute to adverse behavioral outcomes. It has been previously demonstrated that a single administration of these drugs is sufficient to cause ENA in a number of brain regions, including striatum, thalamus, hippocampus, and multiple cortical areas. It remains unclear whether clinically relevant *repeated* drug exposure will further exacerbate ENA or the drugs target only a limited number of vulnerable neurons. During the period of vulnerability to ENA, most brain areas exhibit a low level of naturally occurring apoptosis, presumably affecting neurons that are at a competitive disadvantage. This raises the possibility that only a subset of neurons may be vulnerable to ENA and once they are cleared by the initial drug exposure, no further ENA should be seen following repeated drug exposure. In the present study, we tested this hypothesis.

Methods: Rat pups were exposed to PB (75 mg/kg/d, i.p) daily from postnatal (P) days 5-8. To detect ENA following each subsequent PB dose, we utilized quantification of active caspase-3 immunoreactivity (aCa3 IR) which peaks between 4-8 h following PB injection and is significantly diminished by the time of the next drug exposure. The difference between repeated exposure (e.g., at T=0h and T=24h) determined 8h after initial drug administration (e.g., at T=32h), and the remaining aCa3 IR 32h following exposure at T=0h alone was used to assess the effects of the second PB dose on ENA. The same strategy was used to determine the effects of subsequent PB administrations (at T36h and T48h). Matching injection(s) of the vehicle (saline) were given to control groups. The dorsomedial portion of anterior striatum, an area highly vulnerable to PB-induced ENA, was examined.

Results: We found that a single PB dose on P5 had no effect on ENA, while single exposure on either P6 or P7 increased ENA ~2.5 fold and was comparable to the extent of ENA following repeated (P5-6) PB. However, there was no significant difference in the number of aCa3 positive neurons after repeated doses of PB on P6-7 and following a single P6 exposure when measured on P7.

Conclusions: Our data indicate that repeated administration of PB does not cause a cumulative increase in ENA in striatum, and support the hypothesis that ENA occurs in a limited number of vulnerable neurons. Our results also suggest that possible contribution of ENA to long-term adverse outcomes may be limited to the initial drug exposure during the critical period of brain development. *Support: NIH grant MH079991 and the research grant from the March of Dimes.*

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FINAL RESULTS FROM AN INTERNATIONAL OBSERVATIONAL STUDY OF PREGNANCY OUTCOMES FOLLOWING EXPOSURE TO LAMOTRIGINE

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Rationale: The international registry formed part of an epidemiologic safety program, established in 1992, to monitor pregnancy outcomes in women exposed to lamotrigine.

Methods: Physicians reported exposure to lamotrigine during pregnancy and subsequent outcomes on a voluntary basis. Prospective reporting (prior to any knowledge regarding the possible outcome of the pregnancy) early in pregnancy was encouraged. Major congenital malformations (MCMs) were classified according to the Centers for Disease Control criteria and were reviewed by a pediatrician. The percentage of MCMs was calculated by trimester and according to monotherapy or polytherapy with/without valproate. Conclusions were developed and endorsed by a scientific advisory committee.

Results: Between September 1992 and March 2010, 35 MCMs were observed among 1558 first trimester monotherapy exposures giving a risk of 2.2% (95% CI 1.6 % 3.1%). Assuming a baseline frequency of major defects of 2-3%, the 1558 first trimester monotherapy exposures provide 80% power to detect at least a 1.39 to 1.48 fold increase over the baseline rate. Up to maximum daily doses of 600 mg there was no effect on the rate of major defects. Above 600mg there were insufficient data to assess the effect of increasing dose. The observed risk among 150 lamotrigine and valproate polytherapy exposures was 10.7% (95% CI 6.4% 17.0%) and was 2.8% (95% CI 1.5% 5.0%) among 430 exposures to lamotrigine polytherapy without valproate. No consistent pattern of malformation types was observed.

Conclusions: The Registry did not detect an appreciable increase in the risk of major congenital malformations following first trimester exposure to lamotrigine monotherapy. With a sample size of over 1500 first trimester monotherapy exposures the Registry met its primary objective of excluding major teratogenicity. However, increases in the risk of specific defect types cannot be ruled out. The higher frequency of major malformations following lamotrigine-valproate polytherapy exposure is similar to that reported with valproate monotherapy, though without an internal valproate comparison group conclusions cannot be drawn as to the relative contribution of each drug to that risk estimate. Monitoring of specific birth defects will continue through case control surveillance in the EUROCAT network.

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ACUTE THERAPEUTIC EFFECTS OF CARISBAMATE IN A RAT MODEL OF INFANTILE SPASMS

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Rationale: Infantile spasms are the signature seizures of West syndrome, an epileptic encephalopathy of infancy. Its conventional treatments, adrenocorticotropin hormone (ACTH), steroids and vigabatrin, are not always effective, especially in symptomatic infantile spasms, and may produce adverse effects. Subsequent evolution to other epilepsies and poor developmental outcomes are also encountered in infants who do not respond to current therapies. Therefore, identification of more effective therapies for this syndrome is important. In this study, the efficacy of carisbamate, a novel broad spectrum anticonvulsive drug, was tested in the multiple-hit rat model of symptomatic infantile spasms (DLP model; AECOM patent #2080216183). In this model, spasms are ACTH-refractory and partially sensitive to vigabatrin.

Methods: In the DLP model, spasms appear after a right intracerebral infusion of lipopolysaccharide and doxorubicin at postnatal day 3 (PN3) and p-chlorophenylalanine at PN5. To test the efficacy of carisbamate, we administered a single dose of carisbamate (10, 30, or 60 mg/kg/rat; groups CRS-10, -30 and -60 respectively; 10-13 rats/group) or its vehicle (group VEH; 10 rats) intraperitoneally in PN4 DLP male pups. Separate groups of DLP pups were implanted with epidural EEG

electrodes at PN5-6 and injected with VEH (5 pups) or CRS-60 (7 pups) at PN6 or PN7. Rats were monitored before and after the injection using video (PN4) or video-EEG (PN6-7) recordings and the frequencies of clinical (PN4) or electroclinical spasms (PN6-7) were measured (spasms/hr; least square means ± SE).

Results: At PN4, no significant differences in the frequency of spasms were seen prior to the injections: VEH: 5.91 ± 1.1; CRS-10: 7.47 ± 1.43; CRS-30: 6.53 ± 0.8; CRS-60: 7.53 ± 1.14. During the first 4 post-injection hours, however, spasms significantly decreased compared to VEH group (7.69 ± 1.28), in a dose dependent manner, only in the CRS-30 (3.15 ± 0.79; $P<0.05$) and CRS-60 (3.37 ± 1.71; $P<0.05$) groups but not in CRS-10 (6.09 ± 0.89) pups. No significant mortality was observed at least till PN5, as only 1 pup (group CRS-60) died by PN5.

At PN6-7, no significant differences in the frequency of electroclinical spasms were seen before the injections: CRS-60= 12.8 ± 1.82; VEH= 13.4 ± 2.15. During the first two post-injection hours, the frequency of electroclinical spasms was however significantly suppressed in CRS-60 pups (3.5 ± 1.54) compared to VEH treated pups (11.2 ± 1.83) ($P<0.01$).

Conclusions: Carisbamate displayed acute anticonvulsive effect on spasms after a single injection in an animal model of symptomatic infantile spasms. This acute suppressive effect of carisbamate would have an advantage in the treatment of infantile spasms because early response to spasms has been correlated with a favorable long-term outcome. Carisbamate may be a promising new therapy for symptomatic infantile spasms, including ACTH-refractory spasms.

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ROLE OF LACOSAMIDE AS ADJUNCTIVE TREATMENT OF ADULTS WITH PRIMARY GENERALIZED EPILEPSY

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Rationale: Lacosamide is approved for adjunctive treatment of partial onset epilepsies. The role of lacosamide in treatment of primary generalized epilepsies (PGEs) is not known. Here we present a heterogeneous group of patients with pharmaco-resistant PGEs who were treated with lacosamide add on therapy.

Methods: We present a heterogonous group of 10 patients with pharmacoresistent generalized epilepsy who had adjunctive treatment with lacosamide. This heterogeneous group included four patients with primary generalized tonic clonic seizures, one patient with juvenile absence epilepsy, three patients with juvenile absence epilepsy and generalized tonic clonic seizures, and two patients with atypical absence epilepsy. Clinical characteristics (including age of onset, seizure type, and neurophysiologic characteristic of interictal epileptiform discharges) are summarized in table-1. All patients had normal background EEG, and normal MRI. Eight patients had normal cognitive functions. One patient had mild mental retardation and one patient had learning disability.

Results: The four patients who had primary generalized tonic clonic seizures responded to lacosamide adjunctive therapy in the range of 400-600 mg/day. One of the four patients became seizure-free, and two patients had marked decrease in seizure frequency. One patient maintained seizure freedom during and after switch-over to lacosamide (from felbamate due side effects).

Our only patient with juvenile absence epilepsy became seizure free shortly after initiation of lacosamide. She developed an allergic blotchy rash that resulted in discontinuation of lacosamide in the 6th week of treatment. Following discontinuation she had emergence of absence clusters.

In the three patients with absence epilepsy with generalized tonic clonic seizures, one became seizure free on high doses of lacosamide 600-700 mg/d, one had no further generalized seizure and decrease in frequency of absence seizures. One patient had no response to this medication but became seizure free on Depakote monotherapy.

Neither of the two patients with atypical absence epilepsy had any improvement in their seizure frequency while on lacosamide adjunctive therapy.

Conclusions: Our retrospective data suggests that lacosamide may have a role in adjunctive treatment of pharmaco-resistant primary generalized epilepsies. There is a suggestion that higher doses of lacosamide up to 700 mg/d may be needed for effectiveness. More studies are needed to determine the exact role of this medication and its true spectrum of action.

Table 1. Clinical and EEG Characteristics

IMAGE: tables/908138_T1.jpg

Pt/Dx patient/diagnosis; PGTC primary generalized tonic-clonic seizures; JAE juvenile absence epilepsy; JAE-GTC juvenile absence epilepsy with generalized tonic-clonic seizures; AAE atypical absence epilepsy; A/G age/gender; F female; M male; AOE (yr) age of onset of epilepsy (years); Sz Type seizure type; PM absence seizures; LD/MR learning deficiency/ mental retardation; BG background, IED interictal epileptiform discharges; BF bilateral frontal dominant; SSW spike and slow wave complexes; PS polyspikes.

Table-2. Clinical Response to Lacosamide Therapy

IMAGE: tables/908138_T2.jpg

Pt/Dx patient/diagnosis; PGTC primary generalized tonic-clonic seizures; JAE juvenile absence epilepsy; JAE-GTC juvenile absence epilepsy with generalized tonic-clonic seizures; AAE atypical absence epilepsy; Sz freq seizure frequency; LCM lacosamide; AEDs antiepileptic medications; LEV levetriacetam; LTG lamotrigine; FBM felbamate; ZNG zonisamide; DR Depakote ER; ETX ethosuximide; CBZ carbamazepine; ACZ acetazolamide; DIL dilantin; PRM primidone; RFM rufinamide; GTC generalized tonic clonic seizure; PM absence

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INITIAL POST-MARKETING CLINICAL EXPERIENCE WITH LACOSAMIDE IN ADULT PATIENTS WITH EPILEPSY

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Rationale: We sought to determine the effectiveness of the newly-marketed antiepileptic drug (AED), lacosamide, in adult epilepsy patients.

Methods: The outcomes of adult epilepsy patients who were prescribed lacosamide for additional seizure control are presented herein. The data was compiled by chart review. Responders were defined as having at least a 50% decrease of seizure frequency of all seizures types combined. Seizure types evaluated were complex partial, generalized tonic clonic and atonic. Statistics used were descriptive and Spearman's rank correlations (2-tailed).

Results: Sixty seven patients were evaluated; ages ranged from 18-82, mean 38; 35 were women (52%); mean duration of epilepsy 24 years (range 1-54); mean age of onset 14 years. The patients were refractory having tried up to 16 medications each and VNS with a (mean of 8). The seizure types evaluated were complex partial, 61 patients(91%), generalized tonic clonic, 24 patients (36 %) and atonic, 11 patients (16 %). Lacosamide dose ranges were 50mg - 600 mg per day (278 mg mean dose). The mean duration of treatment was 7 months, range 1-12 months. Forty-six out of 67 patients (69%) were responders. The correlation between dose and responder rate approached significance at 0.093. Twenty-two patients (33%) reported no seizures in the most recent treatment month; this included the only two patients on lacosamide monotherapy. There was no difference in lacosamide dose between patients taking or not taking sodium-channel acting AEDs. Forty two of sixty nine complex/partial (69%), eighteen of twenty four patients with generalized tonic/clonic (75%) and twelve of fourteen patients with atonic seizures((86%) were responders.

Fourteen patients (21%) discontinued; 5 due to side effects (2 for dizziness and 3 for rash), 4 for lack of efficacy and 5 for both. The most frequent side effect was dizziness and discoordination in 22 (33 %) patients, while 10 patients had psychiatric side effects (15 % with mood and anxiety complaints), 2 had headaches (3%) and 3 (4 %) had possible allergic rash. 9 patients (13 %) required dose adjustments secondary to negative side effects.

Conclusions: Our initial results with lacosamide indicate a high responder rate. A higher responder rate was present in those patients who were not taking sodium channel-acting drugs. Allergic rash occurred in 4%.

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EFFICACY OF LACOSAMIDE AS AN ADJUNCTIVE THERAPY IN PATIENTS WITH PARTIAL EPILEPSY, THE FIRST YEAR EXPERIENCE

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Rationale: Lacosamide (LCM) is a newly approved antiepileptic medication (AED) with a novel anticonvulsant activity. The efficacy of LCM has been well demonstrated in patients with refractory epilepsy through the pivotal trials, and LCM is now available in more than 12 countries following the approval by the European Commission in August 2008 and the U.S. Food and Drug Administration in October 2008. However, post-approval experiences are quite limited in real clinical practices where less refractory patients are seen. We evaluate the efficacy of LCM in our clinic population at the Barrow Neurological Institute in order to assess the usefulness of LCM in an outpatient practice setting.

Methods: We identified clinic patients who are taking LCM for partial epilepsy by reviewing clinic records at the Barrow Neurological Institute. The data included patient's gender, age, seizure type, concurrent AEDs, LCM dosages, duration of therapy, and efficacy of LCM. To minimize bias, we excluded patients who had participated in the phase II or III LCM clinical trials in the past. Last observed efficacy information was used to report the efficacy of LCM. The efficacy of LCM was evaluated as responder rates (seizure reduction e"50% during treatment), and responders were further evaluated whether they had reached 75% or greater seizure reduction.

Results: We identified 185 patients who started taking LCM on or after June 3, 2009. The median age of patients was 40.6 years, and 55.7% were female. The mean follow-up duration of patients was 28.9 weeks (median 30 weeks) when efficacy was evaluated. Approximately 66% of patients had tried more than 5 AEDs in the past when LCM was added. LCM was used as monotherapy in 6 patients, and 76.8% of patients were taking 1 or 2 AEDs. Out of 185 patients, efficacy information was available in 152 patients. Overall, 50% responder rate was 53.2% (81/152) and 75% responder rate was 29.6% (45/152). Seizure freedom for more than 6 months was achieved in 6 patients (3.9%). Remaining 43.8% of patients reported less than 50% of seizure improvement. The dosage of LCM was ranged from 100 mg to 400 mg per day with a daily median dosage of 200 mg.

Conclusions: The efficacy of LCM in this study was comparable to the previously reported results in pivotal trials. However, our patient population was somewhat less refractory than previous studies, which may have resulted in higher 50% responder rate. This consistent efficacy result, combined with a favorable pharmacokinetic profile, suggests that LCM is a useful new AED as an adjunctive treatment in patients with partial-onset seizures.

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SEVERITY AND TEMPORAL PATTERN OF LEVETIRACETAM AND LAMOTRIGINE WITHDRAWAL SEIZURES DURING EPILEPSY MONITORING

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Rationale: Antiepileptic drugs (AEDs) are discontinued during epilepsy monitoring unit (EMU) studies in an attempt to precipitate seizures. Some AEDs, such as oxcarbazepine and carbamazepine, need to be slowly withdrawn as they can cause severe withdrawal seizures. Levetiracetam (LEV) and lamotrigine (LTG) are commonly used AEDs that are also routinely discontinued during EMU studies. The aim of this study is to evaluate the severity and temporal pattern of LTG and LEV withdrawal seizures during epilepsy monitoring.

Methods: We identified all patients with epilepsy who were admitted to the Vanderbilt EMU and were on LEV monotherapy, LTG monotherapy or combination LEV and LTG therapy over the last five years. We only included patients who had their AED of interest abruptly discontinued on EMU admission day and patients who had complex partial seizures (CPS) or generalized tonic-clonic seizures (GTC). For each patient, we recorded pre-EMU seizure types and frequency. We noted age, gender, epilepsy onset, epilepsy risk factors, AED total dose and blood levels. We then recorded the number and type of seizures for each EMU day. We compared the seizure frequency before and during EMU for each seizure type. We also compared the first seizure (any seizure, CPS or GTC) occurrence during EMU between the three groups.

Results: A total of 69 patients (45 females) were included in the study. Twenty eight patients were on LEV monotherapy, 10 patients on LTG monotherapy, and the remaining 31 patients were on combination therapy. For all groups, the mean age was 35.9 ± 15.4 years, mean LEV dose was 2148 ± 989 mg and mean LTG dose was 290 ± 129 mg. Mean

blood levels were within the accepted therapeutic range. There was no difference in pre-EMU CPS and GTC frequency, age at onset, or epilepsy risk factors among the three groups. The average EMU stay was 3.9 ± 2.1 days. CPS and GTC during EMU were higher than pre-EMU baseline in all groups ($p<0.05$, Wilcoxon signed rank test). Total CPS during EMU tended to be higher than total GTC. No first time GTC during EMU was reported in 27 patients with no prior history of GTC. In addition, none of the patients had reported status epilepticus. The mean time to first CPS during EMU was 1.9 ± 0.9 days while that of GTC was 2.1 ± 1.1 days. Time for first CPS after LTG withdrawal was the longest compared to the other two groups ($p=0.03$, log-rank test).

Conclusions: Acute discontinuation of LEV or LTG is not associated with severe withdrawal seizures. Withdrawal seizures occur approximately 48 hours following discontinuation. This suggests that LEV or LTG may be safely discontinued 24 hours prior to EMU admission. This approach may help in reducing hospital stay and cost.

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USE OF INTRAVENOUS LEVETIRACETAM IN ACUTE SEIZURE MANAGEMENT IN NEONATES

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Rationale: Neonatal seizures are defined as paroxysmal alterations in neurologic function that can be documented electroencephalographically with or without clinical manifestations. They affect approximately 1 to 4 of 1000 live births in North America and are a major predictor of future adverse neurologic outcomes. Currently approved antiepileptic drugs (AEDs) for neonatal seizures have been shown to have efficacy rates of less than 50% and can have undesirable side effect profiles. Levetiracetam (LEV) is an AED with a novel mechanism of action; the intravenous (IV) form is currently approved as adjunctive treatment for a variety of seizures in patients 16 years of age and older. Only limited data about the efficacy and safety of IV levetiracetam in acute seizure management in children is available and IV levetiracetam is currently not approved for patients <16 years. The goal of this study is to retrospectively assess the efficacy and tolerability of intravenous levetiracetam therapy in acute seizure management during the neonatal period.

Methods: A retrospective chart review was conducted on all term and late preterm neonates who received intravenous levetiracetam at Scott & White Hospital / Texas A & M Health Science Center, Temple, TX between January 2007 and December 2009. Subject data were acquired from electronic medical records. Approval for this retrospective analysis of patient records was given by the hospital's institutional review board.

Results: We retrospectively analyzed 22 neonates 12 females and 10 males with partial epilepsy who received intravenous levetiracetam at our institution . A bolus administration of 50 mg/kg was administered in most patients followed by a maintenance dose of 25 mg/kg every 12 hours. The given dose was infused over 15 minutes to an hour . Nineteen patients (86%) experienced immediate seizure control within one hour of the loading dose. These patients responded to intravenous levetiracetam both electrographically and clinically with improvement seen one hour after commencing the loading dose. No further seizures were recorded while on intravenous levetiracetam in 7 (32%) of neonates after loading. 14 patients (64%) achieved seizure freedom on IV levetiracetam within 24 hours of the loading dose 19 (86%) within 48 hours, and 22 (100%) within 72 hours. Twenty-two patients (100%) were switched to oral levetiracetam and of those, 18 (81%) were discharged home on oral levetiracetam monotherapy. No major immediate or long term adverse effects were reported. Duration of follow up ranges between 2- 6 months.

Conclusions: Intravenous Levetiracetam appears to be safe and efficacious in acute seizure management in neonates.

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PHARMACOLOGICAL CHARACTERIZATION OF A SYSTEMICALLY BIOAVAILABLE GALANIN RECEPTOR (GALR) SUBTYPE-2 PREFERRING ANALOG IN RODENT MODELS OF PAIN AND EPILEPSY

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Rationale: The endogenous neuropeptide galanin and its associated receptors are widely expressed in the CNS and are important modulators of neuronal excitability. We previously described the potent anticonvulsant and analgesic activity of NAX 5055, a systemically bioavailable galanin analog (Bulaj et al., J. Med Chem. 2008, White et al.Neurotherapeutics 2009). More recently we reported on a rational approach to engineering systemically bioavailable galanin analogs that can discriminate between GalR-1 and GalR-2 (Robertson et al., J. Med Chem. 2010). The present investigations provide an extended pharmacological characterization of a prototype GalR-2 preferring galanin analog, NAX 1205-1 (1205-1), in rodent models of epilepsy and pain.

Methods: The anticonvulsant profile of 1205-1 was evaluated in the mouse 6 Hz (44 mA stimulation), maximal electroshock (MES) and the subcutaneous pentylenetetrazol (scPTZ) seizure tests. In addition, 1205-1 was tested against the fully expressed seizure in hippocampal kindled rats. The analgesic effects of 1205-1 were assessed in the mouse formalin and abdominal constriction tests. 1205-1 was also evaluated for its ability to attenuate mechanical allodynia in the rat partial sciatic nerve ligation (PSL) model. For all studies, mice (CF-1) were tested 1 hour following i.p. administration of 1205-1, the previously determined time to peak effect in mice. Rats (Sprague-Dawley) were tested at multiple time-points following i.p. administration.

Results: 1205-1 was potently active in the 44 mA 6 Hz seizure test (ED50 6.6 mg/kg)and was only slightly higher than the previously determined 32 mA stimulation ED50(5.7 mg/kg0. At 1 mg/kg 1205-1 significantly reduced the behavioral seizure score but not the afterdischarge duration in 4 of 8 hippocampal kindled rats tested. 1205-1 was not active against MES and scPTZ evoked seizures at 8 mg/kg. 1205-1 reduced both the acute and inflammatory phases of the mouse formalin pain response (ED50 2.6 and1.7 mg/kg, respectively) and in the abdominal constriction assay (2 mg/kg) it decreased the number of writhes to 15% of control. Lastly, in the PSL model, 1205-1 (1 mg/kg) increased paw withdrawal threshold 2000% of control at 2 hr post-i.p. administration.

Conclusions: These results demonstrate that 1205-1 is potently active in rodent models of acute and chronic pain and refractory epilepsy following systemic administration. Like NAX 5055, this GalR-2 preferring analog possesses a unique profile in seizure models by remaining potently active in two models of partial epilepsy; e.g., the 6 Hz 44 mA test and kindled rat. In contrast, it is not active in the MES or scPTZ tests. Ongoing studies continue to evaluate the therapeutic potential of GalR-2 preferring galanin analogs in models of pain and epilepsy to identify a lead candidate with the most favorable efficacy and safety profile.

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STATED PREFERENCES FOR ATTRIBUTES OF ANTI-EPILEPTIC DRUGS (AEDS) IN PATIENTS WITH UNCONTROLLED EPILEPSY

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Rationale: Employing a methodology new to epilepsy, the purpose is to understand the relative importance of specific attributes of AED treatments and the tradeoffs that patients make between seizure control and tolerability.

Methods: US adult patients with a self-reported physician diagnosis of epilepsy and partial seizure symptoms completed a web-enabled, choice-format conjoint survey. Patients were enrolled based on previous failure of at least 1 AED and currently taking at least 1 AED representing a spectrum of uncontrolled epilepsy. Patients were presented with a series of 9 trade-off questions to evaluate attributes of hypothetical add-on AEDs. AED attributes were selected based on a literature review of controlled clinical trials and included seizure reduction (100%, 75%, 50%, 25%), short-term side effects (dizziness, feeling sleepy, headache, nausea, tremor, double or blurred vision, and skin rash), long-term side effects and their impact on activities of daily living (confusion, memory problems, feeling tired, or mood changes), difficulty urinating, weight change (gain, loss, or no change), dosing frequency, and personal medicine cost. Data were weighted to represent US population with epilepsy and estimated using a combined ranked-logit/conditional-logit model. Data were controlled for baseline seizure frequency.

Results: 209 subjects were analyzed, with a mean age of 44 years; 53% female, 91% white, 70% with some college education, and 29% with disability. Subjects were taking on average 2 AEDs and previously tried an average of 4 AEDs; and reported having an average of 4 seizures in the past 3 months. Based on the trade-off tasks, subjects ranked seizure reduction the most important AED attribute (importance rating=10.0). Remaining attributes ranked in decreasing order of importance were: long-term confusion or memory problems (7.5), short-term side effects (5.1), long-term fatigue or mood changes (3.9), difficulty urinating (2.4), and weight change (2.4). Dosing frequency had no effect. Seizure freedom was 2.5 times more important than long-term fatigue or mood changes, and 4 times more important than a 15-pound weight gain. Long-term confusion or memory problems were 3 times more important than a 15-pound weight gain, and about 2 times more important than long-term fatigue or mood changes. Seizure freedom was 1.6 times more important than a 50% reduction in seizures. Holding everything else constant, patients, on average, valued seizure freedom at $224 (95% CI: $146-$338) a month while the value of a 50% reduction in seizures was $137 ($81-$212).

Conclusions: After controlling for baseline differences in seizure frequency, patients with uncontrolled epilepsy consider seizure reduction the most important attribute, and for which, patients are willing to accept short and long-term side effects.

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CROATIAN PREGNANT WOMEN WITH EPILEPSY AND EFFECTS OF ANTIEPILEPTIC DRUGS EXPOSURE IN THEIR OFFSPRING - SEVEN YEARS OF PROSPECTIVE SURVEILLANCE

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Rationale: The teratogenic effects of intrauterine antiepileptic drugs (AEDs) exposure have been recognized but the relative risks of new AEDs and its long-term neurodevelopmental effects remain poorly understood.

The aim of this study was to follow up pregnancies exposed to AED and their offspring in order to assess teratogenic and neurodevelopmental effect of particular AED of newer generation.

Methods: The study is prospective surveillance of pregnancies in Croatian women with epilepsy from May 2003 to May 2010. The data about pregnancy planning, folate supplementation, frequency of seizures and AED therapy were obtained.

Results: During 7 years we have surveyed 70 pregnancies: 5 were without AED (4 LB (live-births), 1 ongoing pregnancy (OP)). About 59 (90.8%) were exposed to monotherapy: 33 to lamotrigine (LTG): 24 LB, 2 premature deliveries (one with motor delay), 3 spontaneous abortions (SA), 1 artificial abortion, 1 intrauterine death and 3 OP. Twelve LB and 2 SA were exposed to carbamazepine (CBZ), 1 LB was under phenitoine (PHT) and 3 under methylphenobarbital (MPB): 1 SA, 1 LB, 1 preterm LB due to EPH gestosis with peripartal asphyxia. One LB and 1 preterm LB with atrial septal defect, severe psychomotor delay and epilepsy was exposed to gabapentine (GBP), 5 LB and 1 OP were under valproic acid (VP). Six pregnancies were exposed to polytherapy: 1 LB, 1 SA and 1 OP to topiramate (TPM) and VP; 1 still-birth to CBZ and PB; 1 LB with intrauterine growth retardation and dysmorphism to TPM, CBZ, PHT; and 1 OP to VP and clonazepam (CZP).

About 35% of women have planned their pregnancy, but only about 20% have taken folic acid properly (before and during their pregnancies). About 30% of these women had their second or third pregnancy during our survey. After preconceptional counselling during and after their first pregnancies, pregnancy planning in these subsequent pregnancies was above 50%.

Conclusions: We have surveyed pregnancies exposed to LTG, VP, PHT, MPB, GBP, TMP, CBZ and CZP. Pregnancies under polytherapy resulted in larger proportion of complications. Besides 7 spontaneous abortions, 2 still-births, 3 premature deliveries we have

noted 1 possible intrauterine AED effect and 1 premature live-birth with atrial septal defect, psychomotor retardation and epilepsy. Adequate preconceptional counseling in women with epilepsy resulted in higher proportion of pregnancy planning and posibility for periconceptional folic acid intake. Further follow up of all live-births is needed in order to assess the potential neurodevelopmental effect of AED.

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SABRIL® REGISTRY INITIATED TO CHARACTERIZE VISION LOSS ASSOCIATED WITH VIGABATRIN THERAPY

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Rationale: Vigabatrin (VGB) was approved in the United States in August 2009 as adjunctive therapy for adult patients (pts) with refractory complex partial seizures (rCPS) who had responded inadequately to several alternative treatments and as monotherapy for pts 1 month to 2 years of age with infantile spasms (IS). An important safety issue for VGB is the risk of vision loss, which needs further characterization. To manage this risk appropriately, the FDA and Lundbeck Inc. require a comprehensive Risk Evaluation and Mitigation Strategy (REMS), including an ongoing patient registry, which was designed to assess incidence, prevalence, time to onset, progression, and severity of vision loss.

Methods: VGB prescribers and pts are enrolled in the "SHARE" program (Support, Help and Resources for Epilepsy). Participation in SHARE and the registry is mandatory for prescribers and pts. Data on prescriber specialty/location, patient demographics, and clinical characteristics are collected. Pts are assigned unique identifiers, and all data are associated with these identifiers. Regular vision assessments are required throughout VGB therapy. They occur at baseline (d"4 weeks after VGB initiation), at least every 3 months during therapy, and 3-6 months after VGB discontinuation. Visual results are entered into the database. If formal perimetry is conducted, copies of visual field recordings are submitted to SHARE. Spontaneous adverse events (AEs) are not collected via the registry, but rather are treated as post-marketing reports and triaged and submitted to the FDA, as appropriate. Visual assessment data are considered outcome measures, and will be summarized in REMS assessments for the FDA, as required. Mandatory benefit/risk assessments are conducted by treating physicians early in therapy (within 2-4 weeks for IS and 3 months for rCPS). For each patient, if the benefit of VGB exceeds the risk, the prescriber submits the appropriate SHARE form, and the patient then continues in the maintenance phase. Outcomes of benefit/risk assessments are entered into the database, and data are collected as long as pts receive VGB. A steering committee finalized the registry protocol and is overseeing its conduct. The committee has 6 external experts in epileptology, neuro-ophthalmology, and epidemiology, and 3 Lundbeck staff. The committee periodically reviews registry visual function data and spontaneously reported visual function AEs and SAEs, and advises the sponsor on data analysis, and execution of the overall REMS. Analyses will be completed every 6 months during the first year of the registry (2009-10), and then annually for 6 years thereafter.

Results: As of Dec. 2009, 830 pts were enrolled, of which, 538 had IS, 246 had rCPS, and 39 had other diagnoses (as determined by treating physicians). At enrollment, ~50% had previously received or were currently receiving VGB.

Conclusions: The registry provides information on vision monitoring results, including risk factors, which may guide treatment decisions. Encouraging enrollment numbers will be enhanced by ongoing mandatory registry recruitment and will be reported.

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CAREGIVER MEASURES FOR SEIZURE CONTROL AND EFFICACY OF ANTIEPILEPTIC DRUGS FOR CHILDHOOD EPILEPSY: RESULTS OF A PREFERENCE SURVEY

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Rationale: Seizure freedom is most often regarded as the goal of AED therapy, though other measures may represent favorable outcomes for caregivers. We sought to identify caregiver-defined characteristics of successful epilepsy treatment and to quantify efficacy measures as they relate to the perceived success of antiepileptic drug (AED) use.

Methods: A 22-question survey focused on measures of AED efficacy was designed using physician input, patient focus groups, and common clinical trial endpoints. Caregivers of children with epilepsy were administered the survey while attending routine pediatric neurology clinic visits at Emory University. Responses were pooled and frequencies for each question calculated. Responses were further analyzed with regard to seizure type and treatment group, characterized as newly diagnosed/controlled (exposure to 1 AED), adjunctive treatment (exposure to 2 AEDs), or refractory to treatment (exposure to e"3 AEDs).

Results: Two hundred ninety-five surveys were completed with 109 (37%) newly diagnosed/controlled, 84 (28%) adjunctive, and 102 (35%) refractory. The majority (86%) were completed by the patients' parent. The mean patient age was 9.6 years with 66% treated for > 2 years. Seizure freedom and seizure reduction were reported as the two most important outcome measures, respectively, across all seizure types and treatment groups. Two hundred sixteen (76%) respondents considered their seizures "controlled," yet reported a median seizure frequency of 3 per year. Refractory patients tended to accept a higher seizure frequency per year as "control" versus those newly diagnosed (6/yr vs 2/yr). Amongst patients that reported their seizures as uncontrolled, seizure freedom > 6 months and median seizure reduction > 90% maintained for over one year was regarded as evidence of efficacy. These measures were the same regardless of seizure type or treatment group.

Conclusions: While seizure freedom is the most important outcome measure of AED therapy for families and patients, it does not necessarily represent the concept of adequate seizure control. When seizure reduction is the outcome goal, the percent reduction and duration of response representing efficacy is considerably different from outcome measures commonly reported in clinical trials. The goals of treatment and quantification of efficacy measures are similar across all seizure types and treatment groups, suggesting the ultimate goals of treatment do not change for patients as their seizures become refractory to medical treatment. The inclusion of patient-centered outcome goals in clinical trials will likely improve informed decision making and patient expectations when choosing AED treatments.

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STIRIPENTOL: OUR EXPERIENCE

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Rationale: Stiripentol is a novel anticonvulsant that belongs to a family of aromatic allylic alcohols and is thought to have direct anticonvulsant activity related to effects on gammaaminobutyric acid (GABA). It also potentiates the efficacy of other anticonvulsants as a result of its pharmacokinetic interactions. It was authorised in the European Union in January 2007 for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI or Dravet's syndrome) whose seizures were not adequately controlled with clobazam and valproate.

We conducted a retrospective study to evaluate the efficacy and safety of Stiripentol in management of epilepsy in children with Dravet's syndrome and other intractable epilepsy syndromes.

Methods: Retrospective review of electronic case notes of all children treated with Stiripentol from May 2006 to May 2010 in the department of Neurology at the Birmingham Children's Department. The data was supplemented by telephonic questionnaires to parents where required.

Results: A total of 25 children were identified, all with intractable epilepsy. This included 12 males and 13 females with age ranging from 8 months to 13.5 yrs at onset of treatment. They had previously been trialled on 2-14 anti-convulsant medications and 9 had been tried with VNS and /or ketogenic diet with poor seizure control.

16 (64%) had a diagnosis of Dravet's Syndrome. Of this 10(62.5%) were SCN1A mutation positive. 2 were negative for the mutation while results were awaited on 4.

2 children experienced single seizure type while the rest had multiple types of seizures.11 experienced < 10 seizures/day while 8 had > 30 seizures/day.

In 19 children stiripentol was used in combination with either Sodium Valproate and/ or clobazam.

In the SCN1A mutation positive Dravet's group (n=10), 5(50%) experienced significant reduction (50%) in seizure frequency while 4 (40%) showed no benefit and 1 experienced an increase in seizures. Among the SCN1A negative Dravet's (n=2), 1(50%) showed > 50% reduction in seizure frequency while the other child showed no response. In the 4 children in whom the mutation status was not known 3 achieved significant seizure reduction while 1 did not show any response. One child had become seizure free but the benefit was sustained for 4 months only.

In the Non- Dravet's group (n=9), 3(33 %) showed > 50% seizure reduction including one child who was seizure free for 7 months. 6(67%) showed no response.

9(36%) experienced side effects secondary to Stiripentol. This was in the form of sedation (4), appetite / weight problems (3), behavioural problems (2) and raised ferritin(1).

Stiripentol was continued in 18 (72%) while it was withdrawn in 4 cases owing to no benefit and due to side effects in 3.

Conclusions: Stiripentol is effective and safe to use in children with epilepsy. It is effective in reducing seizures not only in children with Dravet's syndrome, but also in other Childhood epilepsy syndromes.

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ANALYSIS OF PREGABALIN USE AND EFFECTIVENESS IN A CLINIC SETTING: A PILOT OF THE WEB-BASED POST-MARKETING ANTIEPILEPTIC DRUG REGISTRY

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Rationale: Clinical trials provide initial information on dosing, titration rates and adverse events (AE); however, data derived from the use of antiepileptic drugs (AED) in clinical practice is also necessary to assist physicians in the effective treatment of seizures. This study of the efficacy and tolerability of pregabalin (PGB) served as a pilot of the Post-marketing Antiepileptic Drug Surveillance (PADS) web-based registry.

Methods: The titration rate and effectiveness of PGB in a large Midwestern epilepsy center was collected and analyzed for patients between 2005 and 2009. A retrospective medical chart review was performed for 95 patients (48 male, 47 female) who ranged from 11 to 86 years old (m=42). Chart reviews were performed for initial and 6-month follow-up visits, as well as seizure and AED history. Data was obtained using the PADS survey, a paper-based system developed by the PADS group, and entered into the pilot web-based PADS Registry. The PADS Registry is designed to compile and store extensive clinically relevant data collected from sites nationwide, thereby providing physicians with large and diverse research populations.

Results: Of the patients prescribed PGB, 72 were diagnosed with localization-related epilepsy, 9 symptomatic generalized, 7 primary generalized, 2 Lennox-Gastaut and 1 juvenile myoclonic epilepsy. Prior to PGB, patients had previously been prescribed an average 6 AEDs (m=5.9). Patients were on an average 3 concomitant AEDs (M=2.7) when starting PGB.

Of 95 patients, 13 (13.7%) achieved seizure freedom after 6 months on PGB. Twenty-three patients (24.2%) reported an improved seizure status; whereas, 27 (28.4%) reported a worsened condition. According to physicians' charts, the global conditions of 40 patients (42.1%) had worsened, while improvement was noted in 12 (12.6%).

Sixty-five patients (68.4%) reported at least one AE of any severity. Of those, 33 (34.7%) experienced severe AEs. Fatigue was the most frequent AE (n=29, 30.5%) with 16 experiencing severe cases, 12 of which resulted in discontinuation of PGB. Fourteen patients (14.7%; 10 female, 4 male) complained of weight gain (m=18lbs) and 12 (12.6%) reported dizziness. Other AEs included ataxia (10.5%), headaches (7.4%), blurred vision (6.3%) and psychomotor slowing (6.3%). Physicians discontinued PGB in 49 patients (51.6%) within 6 months; 35 (71.4%) discontinued due to AEs and 11 (22.4%) due to lack of efficacy. After 6 months, 46 patients (48.4%) remained on PGB; physicians modified the dosage for 12 (12.6%) of those patients.

Conclusions: PGB was effective in improving seizure status in nearly 25% of patients; however, nearly 70% reported AEs. The most frequent AEs were fatigue, weight gain, dizziness, ataxia and headaches. The type of epilepsy syndrome did not affect the discontinuation rates. Additional data is required to determine the tolerability and effectiveness of PGB. This study served as a trial for the PADS Registry, which will expand to include other clinics nationwide in an attempt to compile sufficient data for specific analysis of PGB.

Frequency and severity of adverse events for patients prescribed pregabalin

IMAGE: tables/905813_T1.jpg

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INVERSE AGONISM OF CANNABIMIMETIC (R+)WIN55, 212 ON BEHAVIOR AND SEIZURE THRESHOLD DURING THE JUVENILE PERIOD

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Rationale: Development of spontaneous seizures and neuronal vulnerability are age-dependent. Cannabinoids have anti-convulsant effects on mature neurons under various conditions however; cannabimetics have not been previously tested on immature neurons during the juvenile period. Therefore, we hypothesized that the density and anatomical distribution of endogenously expressed cannabinoid receptors before or after seizures may contribute to the age-related seizure threshold and neuronal vulnerability.

Methods: A single injection of varied doses of (R+)WIN 55,212 (0.5, 1, 5 mg/kg) was administered to postnatal (P) day 20 rats 90 min prior to induction of kainate (KA)-induced status epilepticus. Epileptic behavior and electroencephalography (EEG) recordings were monitored to measure the seizure threshold. Immunohistochemistry and histology were performed with a CB1 specific antibody and hematoxylin and eosin in serial sections, respectively.

Results: Unexpectedly, higher doses of (R+)WIN 55,212 (5 mg/kg) rapidly altered behavior by producing a sustained schizophrenia catatonic-like state; lower doses had minimal or no behavioral effect. After KA administration, seizure scores and EEG recordings were inversely related to (R+)WIN 55,212 dosage whereby higher doses were associated with high seizures scores and synchronous epileptiform activity and low doses with low seizure scores and diminished spiking in the EEG. Immunohistochemistry revealed a dose-dependent reduction in CB1 receptor expression with increasing concentrations of (R+)WIN 55,212 in presence or absence of KA seizures. Nissl staining showed hippocampal injury was only attenuated after low doses of WIN 55,212, consistent with the level of CB1 expression.

Conclusions: Although higher doses produced lasting psychiatric symptoms, low doses abolished seizures, which may be a groundbreaking therapeutic strategy to treat early-life seizures without side effects. Paradoxically, it appears that high doses of (R+)WIN 55,212 fail to prevent seizures and protect CA1 neurons in the juvenile brain because of rapid desensitization, reduced binding efficacy of glutamate and loss of presynaptic activation of CB1 receptors to control excitation.

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THE EFFECT OF FOOD ON THE BIOAVAILABILITY OF USL255, A NOVEL EXTENDED-RELEASE FORMULATION OF TOPIRAMATE

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Rationale: The bioavailability of oral drugs can be influenced by the presence of food. Food can influence absorption of the drug as a result of changes in the gastrointestinal tract or from a direct interaction between the food and the drug. Upsher-Smith Laboratories, Inc. (USL) has recently developed USL255, a novel extended-release formulation of topiramate. This formulation will allow for once daily dosing and may result in diminished fluctuations in plasma concentration, and an improved adverse event profile. Previous pharmacokinetic studies of immediate release topiramate (TPM IR tablet; Topamax®) found that food has no effect on bioavailability; however, the effect of food on USL255 has not yet been reported.

Methods: The pharmacokinetic (PK) parameters of USL255 were investigated in a phase I, randomized, single-center, single-dose, open-label, 3-way crossover study. USL255 200 mg administered in the fasted condition (overnight fast >10 hrs), USL255 200 mg administered in the fed condition (standard high-fat breakfast), and TPM IR 100 mg (b.i.d.) were evaluated. A Williams (6-sequence, 3-period) study design was used to randomize subjects (N = 36) to 1 of 6 treatment sequences, with 6 subjects per sequence. Following treatment, subjects entered a 3-week washout period during which blood samples were collected on the first 14 days. Plasma topiramate concentrations were determined using High Performance Liquid Chromatography (HPLC) with Mass Spectrometry (MS)/MS detection. PK parameters evaluated include, maximum plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$), and half-life ($t_{1/2}$). The effect of consuming a standardized high-fat breakfast was assessed using standard bioequivalence criteria. The *a priori* criterion for the lack of food effect was defined as a 90% confidence interval (CI) of the ratio of the geometric least square mean for $AUC_{0-\infty}$ and C_{max} ($USL255_{fed}$/ $USL255_{fasted}$) that fall within the critical range of 0.8 - 1.25.

Results: The 90% CI for the ratio of geometric least square means of both $AUC_{0-\infty}$ (0.99 [90% CI; 0.89 - 1.09]) and C_{max} (0.97 [90% CI; 0.90 - 1.04]) were contained within the critical range, indicating that the presence of food had no significant effect on USL255 bioavailability. T_{max} was significantly increased in the fed state (24 hr) versus the fasted state (20 hr; P = .04). Furthermore, USL255 was found to be well-tolerated in both fasting and fed conditions.

Conclusions: Results from this initial pharmacokinetic study in healthy volunteers indicate that USL255 is well tolerated and that the overall bioavailability of USL255 is not affected by food; however, the presence of food may slow the time to maximal plasma concentration.

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NEUROPROTECTIVE EFFECT IN RAT HIPPOCAMPUS OF CYCLOOXYGENASE-2 INHIBITOR AND DIAZEPAM AFTER PILOCARPINE-INDUCED STATUS EPILEPTICUS

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Rationale: Status epilepticus (SE) leads to significant mortality and morbidity, and thus new neuroprotective strategies are needed. Diazepam belongs to the first line of therapeutic strategies in SE and is neuroprotective when administered at high doses within 2 h after induction of SE. Cyclooxygenase-2 (COX-2) is an inflammatory enzyme that is induced by epileptic seizures and is associated with neuronal death. The rat model of pilocarpine-induced SE was used to determine if a low dose of diazepam and COX-2 inhibitor (NS-398), when administered together, would decrease the severity of SE and reduce neuronal injury.

Methods: Electroencephalogram (EEG) electrodes were implanted in 25 male Sprague-Dawley rats. SE was induced with lithium-pilocarpine, and continuous EEG and video monitoring were performed for 24 h. Diazepam (10 mg/kg, n = 8), diazepam and NS-398 (10 mg/kg, n = 8), or vehicle (0.5% methylcellulose, n = 9) were injected at 30 min after the first motor seizure. Diazepam and control groups received vehicle 6 h later, while the diazepam+NS-398 group received NS-398. The severity of SE, evaluated as EEG power in the ã-band, was analyzed using an automated algorithm. FluoroJade B staining in the dorsal hippocampus at 24 h after SE was analyzed semi-quantitatively in CA1, CA3 and hilus of the dentate gyrus.

Results: Analysis of the electrographic data showed no difference between the control, diazepam and diazepam+NS-398 groups; severity of electrographic SE in the ã-band was similar in the three groups. Diazepam, at 10 mg/kg, did not have significant neuroprotective effect when injected at 30 min from first motor seizure. In rats treated with diazepam+NS-398, compared to vehicle rats, neuroprotection was significant in CA1 (61±3%), CA3 (63±6%) and hilus of the dentate gyrus (60±12%), ANOVA followed by Dunnet's test, $p<0.05$. Compared to diazepam alone, the combination of diazepam and NS-398 led to significant neuroprotection in CA3 (57±5%) and hilus of the dentate gyrus (55±10%), $p<0.05$.

Conclusions: We previously reported that the COX-2 inhibitor, when administered alone, decreased neuronal damage in the hippocampus (CA3: 27±4% and hilus of the dentate gyrus: 27±3%) without a detectable effect on the seizure activity associated with SE. The present data suggest that the combination of low-dose diazepam (10 mg/kg) with NS-398 leads to more effective neuroprotection in the hippocampus than NS-398 alone, and this occurs without an effect on the electrical activity during SE.

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AGGRAVATION OF ABSENCE SEIZURE RELATED TO LEVETIRACETAM

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Rationale: Recent data have reported the effectiveness of levetiracetam (LVT) on generalized seizures. Among them, it seems that LVT can be successfully used to treat absence seizures. Many antiepileptic drugs (AEDs) have been occasionally reported to paradoxically aggravate some seizures. Among the various epilepsy syndromes, idiopathic generalized epilepsy seems more prone to drug-induced worsening.

Methods: We retrospectively identified patients with aggravation of absence seizures using LVT from the databases of 2 pediatric neurology departments (Robert-Debré, Paris and Amiens; France). We also used the prospective data from an open-label clinical trial performed in a third pediatric neurology department (Necker, Paris; France).

Results: We included 6 patients. The patients were treated for the following epilepsies: n=2 childhood absence epilepsy, n=3 juvenile absence epilepsy and n=1 epilepsy with myoclonic absences. All of them have had, at least, an aggravation of the absences with a causal and temporal relationship between introduction of the drug and the detrimental effect. The aggravation disappeared when LVT was decreased or was withdrawn.

Conclusions: This report highlights that LVT may aggravate epilepsy with absence seizures. This effect should be known to provide rapid and adequate management. Failure to recognize seizure aggravation by an AEDs has a significant impact on the patient's quality of life.

IMAGE: tables/903801_T1.jpg

ESM: Ethosuximide; GTCS: generalized tonic clonic seizure; LTG: lamotrigine; VPA: valproate; Sz: seizure

2.175

LOWERED PLATELET COUNTS IN LEVETIRACETAM TREATED EPILEPSY PATIENTS

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Rationale: Haematological side effects are among the most commonly reported adverse reactions in patients treated with several of the old antiepileptic drugs (AEDs), i.e.carbamazepine (CBZ), valproate (VPA) and phenytoin. These effects develop insidiously over time, but may have serious consequences for the patient and can even be life-threatening.

Little is known about haematological side effects of the newer AEDs. There have been only a few sporadic reports of isolated neutropenia or thrombocytopenia associated with the use of lamotrigine (LTG) and levetiracetam (LEV). The aim of our study was to investigate hematological changes in patients treated with the newer AEDs LEV and LTG, compared to the older AEDs VPA and CBZ.

Methods: : In a cross-sectional study of 251 patients with AED monotherapy for at least six months, we assessed the effect of CBZ (n=90; females/males: 29/61), VPA (n=29; females/males: 14/15), LEV (n=52; females/males: 21/31) or LTG (n=80; females/males: 43/37) on hemoglobin (Hb), white blood cells (WBC) and platelets. Additionally, the results were compared to 79 healthy controls (females/males: 43/36). The subjects were between the age of 18 and 45 years old and recruited from hospitals in the South Eastern part of Norway and the Department of Neurology of the University Hospital Innsbruck, Austria.

Results: The study showed significantly lower platelets count in both men and women under LEV monotherapy. Among patients on LEV monotherapy, platelets were 14 % lower (40,68 x 1012 / L lower) when compared to the control group (95% CI ranging from 20,2-61,2 x 1012 / L). There was no difference in sex or age. Other changes were small, with a statistically significant higher WBC in women with either CBZ,

VPA, LEV or LTG, higher Hb in women with LEV and lower Hb for men treated with CBZ.

Conclusions: Both men and women treated with LEV monotherapy have lower platelets count than healthy controls, with no difference in Hb or WBC. The effect of LEV on platelets count has not been described in larger, clinical studies to date. Recent case reports, however, have raised concern of a possible risk for bleeding during LEV treatment due to altered thrombocyte function in selected patients (1,2). The effect of LEV on platelet function should therefore be explored further.

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2.176

PHARMACOKINETIC EQUIVALENCE BETWEEN IMMEDIATE-RELEASE TOPIRAMATE AND USL255, A NOVEL EXTENDED-RELEASE FORMULATION OF TOPIRAMATE

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Rationale: Plasma concentrations of antiepileptic drugs (AEDs) can fluctuate between dosing intervals. This fluctuation can lead to increased side effects during peak concentration levels (C_{max}) or break-through seizures at the trough concentration (C_{min}). While dosing multiple times in a day can reduce the time interval between drug intakes and minimize the fluctuations in plasma concentration, medication compliance may be lessened. Extended-release (ER) formulations of AEDs that provide stable serum concentrations over time with less frequent treatment administration have been developed. The pharmacokinetic (PK) characteristics of USL255, a novel ER formulation of topiramate developed by Upsher-Smith Laboratories, Inc., were compared to immediate-release topiramate (TPM IR tablet; Topamax®).

Methods: PK parameters of USL255 were investigated in a phase I, randomized, single-center, single-dose, open-label, 3-way crossover study. USL255 200 mg administered in the fasted condition (overnight fast e"10 hrs), USL255 200 mg administered in the fed condition (standard high-fat breakfast), and TPM IR 100 mg (b.i.d.) were evaluated. A Williams (6-sequence, 3-period) study design was used to randomize subjects (N = 36) to 1 of 6 treatment sequences, with 6 subjects per sequence. Following treatment, subjects entered a 3-week washout period during which blood samples were collected on the first 14 days. Plasma topiramate concentrations were determined using High Performance Liquid Chromatography (HPLC) with Mass Spectrometry (MS)/MS detection. PK parameters evaluated include maximum plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$), and half-life ($t_{1/2}$). To show equivalence of topiramate exposure, the 90% confidence interval (CI) of the ratio of the geometric least square means (USL255/TPM IR) for $AUC_{0-\infty}$ must be contained within the standard critical range (0.8 - 1.25). Similarly, the upper limit of the 90% CI of the USL255/TPM IR ratio for C_{max} should be less than 1.25.

Results: Topiramate exposure did not differ between USL255 and TPM IR formulations. The 90% CI for the ratio of geometric least square means for $AUC_{0-\infty}$ (0.91 [90% CI; 0.87-0.95]) was found to fall within the critical 0.8 - 1.25 range. In addition, the upper limit of the 90% CI of USL255/TPM IR ratio for C_{max} was less than 1.25 and the point estimate ratio was less than 1.0 (0.70 [90% CI; 0.65-0.74]), indicating that USL255 has a lower C_{max} than TPM IR. TPM IR achieved T_{max} 2 hrs after administration of the second dose (14hr) and the T_{max} for a single dose of USL255 was approximately 20 hrs. USL255 and TPM IR were both well-tolerated by the healthy volunteers who participated in this study.

Conclusions: A single-dose of USL255 demonstrated exposure of topiramate equal to TPM IR but had a lower maximum plasma concentration than TPM IR. Taken together, these data suggest USL255 may improve upon the PK profile of the currently available IR formulation.

2.177

ARK™ IMMUNOASSAYS FOR ANTIEPILEPTIC DRUGS: GABAPENTIN, LAMOTRIGINE, LEVETIRACETAM, TOPIRAMATE, ZONISAMIDE

Kenneth C. Kasper, K. Chung, B. Moon, J. Nguyen, A. Orozco, J. Valencia and J. Valdez (ARK Diagnostics, Inc., Sunnyvale, CA)

Rationale: Therapeutic monitoring of the current new generation of antiepileptic drugs (AEDs) is benefitted by the advent of immunoassays for their quantitative measurement in serum or plasma on automated clinical chemistry analyzers available in the central laboratory. Homogeneous enzyme immunoassays for the measurement of gabapentin, lamotrigine, levetiracetam, topiramate, and zonisamide were developed by ARK Diagnostics, Inc.

Methods: The performance of these assays on the Roche/Hitachi 917 automated clinical chemistry analyzer is described. Six-level calibration for gabapentin (0 to 40 µg/mL), lamotrigine (0 to 40 µg/mL), levetiracetam (0 to 100 µg/mL), topiramate (0 to 60 µg/mL), zonisamide (0 to 80 µg/mL) and tri-level controls for each analyte were used to establish precision and other performance.

Results: Total (within-laboratory) precision of tri-level controls ranged respectively for gabapentin (3.6 to 5.6%), lamotrigine (4.1 to 6.1%), levetiracetam (3.7 to 4.5%), topiramate (2.7 to 4.3%) and zonisamide (4.5 to 5.3%). Analytical recovery and endogenous interference studies demonstrated performance within 10% of expected levels. Lower limits of quantitation for gabapentin (0.5 µg/mL), lamotrigine (0.85 µg/mL), levetiracetam (2.0 µg/mL), topiramate (1.5 µg/mL), and zonisamide (2.0 µg/mL) were based on accurate recovery within 15% and precision within 20% CV. Using Passing Bablok regression analysis for method comparison: ARK Gabapentin = 0.96 LCMS/MS - 0.06 (r^2 = 0.96, n=183, range 1.0 to 39.0 µg/mL); ARK Lamotrigine = 1.01 HPLC + 0.37 (r^2 = 0.97, n=193, range 1.00 to 36.7 µg/mL); ARK Levetiracetam = 1.01 LCMS/MS + 0.25 (r^2 = 0.97, n=305, range 2.0 to 86.4 µg/mL); ARK Topiramate = 0.99 GC - 1.19 (r^2 = 0.97, n=28, range 5.3 to 53.0 µg/mL); ARK Topiramate = 0.99 FPIA - 0.17 (r^2 = 0.99, n=113, range 1.5 to 53.4 µg/mL); ARK Zonisamide = 1.13 HPLC + 0.26 (r^2 = 0.96, n=110, range 5.1 to 46.1 µg/mL).

Conclusions: ARK assays measured AEDs in serum or plasma as demonstrated on the Roche/Hitachi 917, and correlated well with comparative reference methods. All reagents, calibrators, and controls are supplied as stable liquids, ready-to-use, and are well-suited for routine therapeutic drug monitoring (TDM).

2.178

DEVELOPMENT OF A WEB-BASED, POST-MARKETING SURVEILLANCE REGISTRY FOR ANTIEPILEPTIC MEDICATIONS

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Rationale: The importance of post-marketing drug surveillance is to monitor negative side effects and identify superior treatment options. Performing continuous comparative effectiveness trials will allow physicians to strive for highest quality of care by identifying the most effective, safest and cost-effective methods for treating seizures. Our goal is to establish and implement an internet-based post-marketing antiepileptic drug (AED) registry that will provide clinicians and researchers with the ability to answer important questions about drug efficacy, safety and concomitant drug interactions ultimately leading to improved health care of persons with epilepsy.

This goal of this project is to design and initiate a multi-center, collaborative, post-marketing AED surveillance registry. The internet-based design of the PADS database registry will allow multiple clinics to collect standardized clinically relevant information about newly released AEDs across a large and diverse patient population.

Methods: This internet-based registry was adapted from the design and concept of the paper-based system utilized in studies conducted by the Post-marketing Antiepileptic Drug/Device (PADS) group. A team of research coordinators, web application developers and epileptologists worked to develop an infrastructure that can support multi-center data collection and oversight, including the use of a centralized IRB, creation of a secure web application and formation of a data-coordinating center (DCC).

Results: A web application (www.padsregistry.org) was developed and piloted using patient data from the Regional Epilepsy Center. The website is designed to keep patient data secure by assigning study personnel specific levels of access and password logins. In addition to capturing the occurrence of adverse events, the database contains efficacy and tolerability data from a diverse group of patients often under-represented in clinical trial samples. These patients include: people with rare disease states, racial minority groups, pregnant women, children and adolescents.

Conclusions: The uniqueness of this registry lies in the potential to conduct high quality comparative effectiveness studies by collecting a large volume of data across multiple clinical sites. The registry will accelerate the advancement of research and treatment options for a large and diverse population of patients by quickly identifying efficacy, tolerability and adverse events of post-marketed AED's by identifying which subgroups of patients who could benefit from each therapy.

The PADS registry intends to expand into clinic sites outside of the Regional Epilepsy Center and hopes to involve multiple investigators, including members of the original PADS group. Involving a collaborative group of investigators from multiple sites will provide a very large and diverse patient population, which will promote accurate evaluations of the use and effects of newly released AEDs within realistic clinical settings.

IMAGE: images/904388_A.jpg

IMAGE: images/904388_B.jpg

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DEVELOPMENT AND OPTIMIZATION OF EXTENDED-RELEASE FORMULATIONS OF TOPIRAMATE

L. Lambrecht, M. B. Halvorsen, M. J. Boulware, Wesley Mark Todd and J. Carrithers (Upsher - Smith Laboratories, Inc., Maple Grove, MN)

Rationale: Plasma concentrations of antiepileptic drugs (AEDs) can fluctuate between dosing intervals. This fluctuation can lead to increased side effects during peak concentration levels (C_{max}) or break-through seizures at the trough concentration (C_{min}). While dosing multiple times a day can reduce the time interval between drug intakes and minimize the fluctuations in plasma concentration, medication compliance may be lessened. Extended release (ER) formulations of AEDs that provide stable serum concentrations over time with less frequent treatment administration have been developed. Once-daily (QD) extended-release (ER) formulations of topiramate (TPM) were developed by USL to potentially address these concerns. The *a priori* pharmacokinetic (PK) goals of TPM ER QD formulations were: 1) C_{max} for TPM ER d" C_{max} for TPM immediate-release (IR) administered every 12 hours (q12h) at simulated steady-state (SS), 2) C_{min} for TPM ER e" C_{min} for TPM IR q12h at SS, 3) AUC_{0-t} for TPM ER that is equivalent for extent of exposure (90% confidence intervals [CI] between 80% - 125%) to TPM IR q12h at SS.

Methods: Numerous TPM ER QD formulations were internally developed and evaluated in PK studies. All studies were single-dose, crossover designed trials comparing TPM ER test formulations to TPM IR. Each study included a 14-day PK sampling period. TPM concentrations were measured in plasma using High Performance Liquid Chromatography (HPLC) with Mass Spectrometry (MS)/MS detection. The PK parameters (C_{max}, AUC, T_{max}, $t_{1/2}$) were calculated at single-dose (SD) and at SS using PK data modeled to SS using nonparametric modeling. Additionally, C_{min} was determined from modeled SS data. Point estimates (PE) of the ratio between the test formulations and TPM IR with corresponding 90% CI were calculated.

Results: PK studies showed that all of the formulations met one or more of the *a priori* PK goals. Several of the formulations, dosed QD, had C_{max} that were lower, C_{min} that were higher, and equivalent extent of exposure at modeled SS compared to TPM IR dosed q12h. Formulations with delayed T_{max} were found to be eliminated from the body prior to complete absorption of the active ingredient.

Conclusions: It is possible to develop TPM ER QD formulations that have improved PK characteristics to TPM IR q12h.

2.180

SAFETY OF LACOSAMIDE FOR HOSPITALIZED PATIENTS WITH SEIZURES

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Rationale: Lacosamide (LCM) is a novel antiepileptic drug with favorable properties including intravenous (IV) formulation, minimal hepatic metabolism, minimal protein binding and no adverse respiratory or hemodynamic effects. Little is known regarding LCM therapy in hospitalized patients with regard to hemodynamic profile and adverse events.

Methods: We retrospectively reviewed electronic medical records for patients treated with LCM at a single tertiary-care academic medical center (Mayo Clinic Florida) from July 2009 to January 2010. Collected data included age, sex, indication, dosing regimen, primary medical service, concomitant AED therapy, and documented seizure activity (clinical diagnosis or EEG). Safety was assessed by pre- and post-drug hemodynamic parameters (heart rate, systolic blood pressure, diastolic blood pressure, mean PR interval) as well as laboratory parameters including serum creatinine (SCr) and liver function tests (LFTs). Adverse drug reactions or drug interactions were assessed as reported by clinical documentation.

Results: We identified 32 patients treated with LCM during the study period (17 treated in the ICU). Twelve patients received LCM for seizure prophylaxis whereas 20 received LCM for seizure treatment. Twenty-five patients received LCM by IV route, 19 underwent IV to PO, and 7 patients received LCM by PO route only. The majority of seizure patients (n=20; 62.5%) received LCM as adjunctive therapy whereas 12 patients (37.5%) received LCM as monotherapy. No hemodynamic instability, serious cardiac arrhythmias, cardiac or respiratory arrest occurred in any patient who received LCM. ECGs in selected patients demonstrated a mean (SD; range) PR interval of 185.5 ms (33.1; range 148-254) after drug initiation compared to a baseline of 179.3 ms (47.5; range 80-274). Laboratory data revealed no clinically significant changes in baseline and 24hr post-drug SCr or LFTs.

No drug interactions were identified and adverse events were reported in three patients (9.4%). One patient complained of “dizziness and nausea”, one had alteration in mental status with PR interval prolongation (212 ms vs 178 ms baseline). One patient experienced thrombocytopenia of unknown etiology while receiving LCS. All adverse events resolved after drug discontinuation.

Conclusions: LCM demonstrated a favorable hemodynamic safety profile for hospitalized patients. Nine percent experienced adverse events while receiving LCM that resolved in all cases upon drug discontinuation. Future prospective studies are needed to assess safety of LCM in hospitalized patients.

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INTER-PREGNANCY VARIABILITY IN LAMOTRIGINE PHARMACOKINETICS IN A SINGLE PATIENT

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Rationale: Lamotrigine is a commonly prescribed medication given its relatively benign side effect profile and stable steady state levels. The decrease in serum Lamotrigine levels in pregnancy secondary to increased clearance and consequently increased risk of seizures has been well documented. In few of these studies, a singular patient with serial pregnancies have been observed and studied - two patients with two pregnancies each and one patient with two pregnancies and one with three pregnancies. Though all studies had detailed analysis of patient population pregnancies, there was no comprehensive inter-pregnancy comparison for a singular patient. Here we present variation in Lamotrigine pharmacokinetics in serial pregnancies in the same patient. Our study was prompted by the observation that a higher dose of Lamotrigine was needed with each subsequent pregnancy to achieve the same serum level.

Methods: N.H is a 35 year old female with localization related epilepsy and poorly characterized seizures. Since 2007 she has had three successful pregnancies and has been maintained on Lamotrigine throughout. Apparent clearance was considered as the best measure of Lamotrigine variability as it also included weight of the patient.

Apparent Clearance = Daily dose (mg/kg)/ Serum Lamotrigine concentration (mg/L)

Weights were obtained from neurology and obstetric clinic notes and hospital admissions. Due to frequent telephone correspondence daily dose was available for every week that was included in the study. Baseline was considered as 6 weeks prior to conception for pregnancy 1, 13 weeks prior to conception for pregnancy 2 and 6 weeks postpartum for pregnancy 3. For every Lamotrigine level, if a corresponding weight was not available it was calculated using linear extrapolation. A two way analysis of variance with main effects of trimester and pregnancy number followed by Fisher’s protected least significant difference tests were applied.

Results: Two way analysis of variance showed a statistically significant effect of trimester but no significant effect of the pregnancy number. Fisher’s test found that clearance was elevated in the second and third trimester as compared to the baseline and first trimester. There was no significant interaction, indicating that there was no effect of pregnancy number on the changes in clearance seen over the trimesters. There was a non-significant trend towards decreased clearance during second and third trimester with serial pregnancies.

Conclusions: Contrary to our initial assumption, there was a trend towards decreased clearance with subsequent pregnancies. This was a retrospective observational study and it is likely that statistical significance was not achieved due to lack of more frequent serum Lamotrigine levels. A prospective study with more frequent serum Lamotrigine levels would be needed to further delineate the differences in pregnancies.

IMAGE: images/905370_A.jpg

IMAGE: images/905370_B.jpg

2.182

VALENCIAN COMMUNITY LACOSAMIDE EXPERIENCES COLLECTION GROUP(RELACOVA)

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Rationale: Lacosamide is a new antiepileptic drug (AED) commercialized as add-on therapy for partial epilepsy in Spain since September 2010. An independent group, called RELACOVA, was created to collect the experiences with this new drug in clinical practice.

Methods: The group has been constituted by neurologists/ epileptologists from different general hospitals and epilepsy Units in the Valencian Community (Spain). Data from patients were prospectively collected according to clinical practice. All the patients in which lacosamide was introduced according to the clinician criteria were included. A database was created to collect the information at the day of introduction of the drug, at 3 months, at 6 months and at 12 months. These data included age, gender, epilepsy and seizure type, number of seizures per month, lacosamide dosage, concomitant and prior AEDs, efficacy and side effects.

Results: So far, one hundred and forty-nine patients have been included in the follow-up, ninety-one percent of wich were refractory. One hundred patients have been followed for 3 months and thirty-seven patients for 6 months. The efficacy analysis at 3 months has showed 58% of responders (e" 50% seizure reduction) (21% of them were seizure-free) and at 6-months the rate of responders was 27% patients (8% seizure free). Dizziness was the most frequent adverse event. Six percent of patients discontinued the medication because of side-effects at 3-months and none at 6 months. Concomitant AEDs were reduced in 18% of patients.

Conclusions: The preliminary results of lacosamide in clinical practice (in a refractory epilepsy population) have shown promising efficacy data and few side effects, severe enough to discontinue only in 6% of patients. A longer follow-up and the collection of more patients are required to support the results.

2.183

EVIDENCE FOR THE NOOTROPIC EFFECTS OF ACTHAR GEL (ACTH) IN EPILEPTIC KCNA1-NULL MICE

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Rationale: Rationale: Acthar Gel (ACTH) - containing a 39 amino acid peptide derived from pro-opiomelanocortin - is efficacious in the treatment of infantile spasms, an age-dependent catastrophic epileptic syndrome. A retrospective clinical study has suggested that ACTH might enhance cognitive function (PMID:19348622), but it is uncertain whether this occurs independent of its anticonvulsant activity. We asked whether ACTH might exert anticonvulsant and/or nootropic effects in intrinsically epileptic Kcna1-null mice.

Methods: Methods: Heterozygous breeding pairs generated Kcna1-null (KO) mice. Two parasagittal electrodes and subcutaneous wireless transmitters were implanted at P28. Following a 2-day recovery period, baseline seizure activity was assessed over 72 hrs using wireless video-EEG recording techniques. Following the initial recording period, KO mice (n=4) were treated with 4 IU/kg ACTH IP four times daily for 7 days followed by a second 72-hr video-EEG recording (P37-40). An age-matched group of KO mice (n=3) were injected with saline under the same experimental conditions. After video-EEG monitoring, both ACTH-treated and control KO mice were sacrificed and long-term potentiation (LTP) was evoked in CA1 hippocampus by high frequency stimulation (HFS, 1 sec, 100 Hz) using standard electrophysiological techniques. Excitatory post-synaptic potential (EPSP) amplitudes during the maintenance phase of LTP were compared amongst the 2 cohorts using ANOVA.

Results: Results: Baseline video-EEG data revealed an average of 2-3 spontaneous generalized seizures per day. Interestingly, no significant changes in seizure frequency were detected following ACTH treatment. HFS induced normal LTP responses in CA1 hippocampal slices from WT mice; however, LTP maintenance was significantly impaired in KO mice. ACTH produced a partial but significant recovery of LTP maintenance in KO animals; EPSP amplitudes were significantly different ($p<0.05$) between WT vs. KO and ACTH-treated vs. KO groups.

Conclusions: Conclusions: ACTH exerts partial protective effects against intrinsic LTP impairment in Kcna1-null mice, suggesting that this peptide may provide nootropic effects in epileptic brain. Moreover, ACTH does not significantly reduce the frequency of spontaneous recurrent seizures in this KO model, arguing against seizure reduction being a confounding variable in our LTP experiments. Further studies involving additional animal models are necessary to further delineate the functional neuroprotective effects of ACTH.

Supported by Questcor Pharmaceuticals, Inc.

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EFFICACY AND TOLERABILITY OF CLASSIC VERSUS NEW GENERATION ANTIEPILEPTIC TREATMENT OF PATIENTS WITH LOW GRADE BRAIN TUMORS AND EPILEPSY

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Rationale: Patients with low grade brain tumors (LGBT) frequently experience seizures that can significantly affect their quality of life.

However there is little evidence about seizure management and patient's cancer and life impact among this group.

The purpose of this study was to analyze efficacy and tolerability variables of antiepileptic (AEDs) treatment of a group of patients with LGBT associated to seizures.

Methods: We retrospectively analyze thirty patients with LGBT.

Data were collected regarding patient's epidemiological characteristics and oncology and epilepsy history.

Results: Mean age at diagnosis was of 38.3 %, 56.7% were male.

The major histologic diagnosis was low grade astrocytomas (36.7%).

Most of the patients experienced seizures (86.7%), on 66.7% it was the LGBT debut symptom. Previous tumor diagnosis, 6.7% were epileptic.

Over 93.3% patients were initially treated with classic generation AEDs, after two years of follow up there were only 56.7%, the rest of them received new AEDs.

The main reason of classic AEDs replacement for new ones was adverse effects at 6 months follow up and chemotherapy interaction at 24 months (p:0.000).

Initially only 14.3% were supervised by an epileptologist.

The effectiveness in seizure control showed no significant difference between classic and new generation AEDs treatment ($p>0.05$).

However tolerability variables seem to be influenced by AEDs treatment election. Those patients with LGBT and seizures treated with new AED experience less adverse effects and had better quality life's punctuations (Karnofski index, KI) reaching statistical significance ($p<0.05$).

The percentage of patients with an KI e" 80 was of 100% in those treated with new generation AEDs and only of 64.7% on classic AEDs treatment group (p:0.017).

Conclusions: Our findings indicate a high rate of new generation AEDs' tolerability among this group compared with classic ones, with no efficacy difference on seizure control.

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OCULOGYRIC CRISES SECONDARY TO LAMOTRIGINE OVERDOSAGE

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Rationale: Tics, chorea, downward deviation of eyes, oculomotor apraxia, blepharospasm, involuntary excessive eye blinking, but not oculogyric crisis (OGC) have been reported as manifestations of Lamotrigine (LTG) overdosage . Here we report a case series of four patients (3 males and a female) with LTG induced OGC.

Methods: Patients who developed OGC on increased doses of LTG (due to inadvertent ingestion and/or dose escalation), who did not have preexisting movement disorders, and who had no recurrence of the episode after the reduction of dose of LTG were included. Retrospective review of the charts was done.

Results: Average age was 12.25 years (range 3 -25). Two patients had partial seizures, one had generalized tonic-clonic seizures and one had absence seizures. In all the cases, OGC was the main manifestation that brought the patient to medical attention. The number of OGC episodes ranged from 1 to 20 per day for 2 days to 3.5 months. The duration that each episode lasted ranged from 2 seconds to 4 hours. Mean blood level of LTG before the period of toxicity was 7mcg/ml (6-12), during was 15.5mcg/ml (9-20) with a mean dose of 13mg/kg/day (7-25), and after dose reduction was 8mcg/ml (7-9). Mean duration of LTG therapy before the occurrence of 1st episode was 4.5 months. Other antiepileptic drugs used concomitantly include clonazepam (2 patients), ethosuximide (1), valproate (1), topiramate (1) and levetiracetam (2). Associated symptoms were dizziness, lightheadedness, nausea, sleepiness and tremulousness.

Conclusions: OGC is one of the manifestations of LTG toxicity

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ANTIEPILEPTIC DRUGS AND SIDE EFFECTS IN ADULTS WITH EPILEPSY IN TERTIARY CARE

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Rationale: The choice of antiepileptic drugs (AEDs) varies according to clinical setting and sociodemographic factors. Few studies have examined the use of AEDs in Canadians with epilepsy. We examined the type of AED, associated side effects, and recommendations to switch AEDs in a large consecutive cohort of patients seen in an epilepsy tertiary care program.

Methods: The University of Calgary Division of Neurology is the main tertiary referral centre for adults with epilepsy, serving 1.3 million people. We prospectively captured data on all consecutive adults with the diagnosis of epilepsy at the first encounter in the outpatient epilepsy program, using a validated data capture and verification system. We analyzed current and past use of AEDs, proportion of patients with side effects on each AED, predictors of side effects, and recommendations to change AEDs after the 1st encounter. Descriptive and cross correlation statistics were used to assess pertinent associations.

Results: In 687 consecutive patients (52% women) the mean age and duration of epilepsy was 40 and 12 years respectively, 64.1% had focal epilepsy, 23% had idiopathic generalized epilepsy, and 21% were seizure free in the past year. At the 1st encounter, 83% were on AEDs, and of these, 71% were on monotherapy, while 21% were on 2, 6% on 3, and 2% on >4 AEDs. In the past, 48% had been on monotherapy and 52% on polytherapy. Of 18 different AEDs used, the commonest (median dose) were phenytoin (23%, 350mg), carbamazepine (21%, 800mg), valproate (13%, 1000mg), lamotrigine (12%, 200mg) and clobazam (8%, 20mg). The least commonly used AEDs (<20% of patients) were clonazepam, ethosuximide, felbamate, gabapentin, oxcarbazepine, pregabalin, primidone and vigabatrin. Side effects (SE) of AEDs occurred in 65% of patients at some point. On monotherapy, 48% had SE in the past and 28% at the initial visit. In 23%, SE occurred with every drug tried. AEDs most commonly associated with SE were phenobarbital (38%), topiramate (34%), levetiracetam (33%), carbamazepine (30%), and phenytoin (29%). Factors associated with a significantly higher risk of SE were female gender (RR 1.42, $p < 0.001$), having a learning disorder (RR 1.4, $p<0.01$), and having complex partial (RR 1.2, $p = 0.01$), generalized tonic clonic (RR 1.3, $p=0.001$) or absence seizures (RR 1.3, $P=0.05$). Factors associated with a significantly lower risk of SE were non-epileptic seizures (RR 0.45, $p=0.02$), and syncope (RR 0.42, $p=0.003$). Changes in AEDs were made in 24% of patients during the first encounter. The commonest AEDs started were lamotrigine (29%), carbamazepine (25%), levetiracetam (16%), valproate (13%), and clobazam (10%).

Conclusions: Side effects were extremely common (65%) in this population, and 23% patients had SE with every AED tried. Unexpectedly, gender and learning disability are associated with a higher prevalence of side effects. Management was suboptimal in almost one quarter of patients and required AED changes during the first encounter. These findings highlight the importance of carefully assessing side effects in these patients.

2.187

LACK OF ASSOCIATION OF POLYMORPHISMS IN THE CYTOCHROME P450 (CYP) 2D6 GENES IN INTRACTABLE CHILDHOOD EPILEPSY

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Rationale: Cytochrome P450 (CYP) 2D6 is the principal enzyme responsible for the metabolism of numerous clinically important drugs including phenytoin. CYP2D6*3 and *4 genotypes in CYP2D6 gene are found to be related with poor metabolism of these drugs. We hypothesized that polymorphisms in this gene may possibly be related to drug resistance in epilepsy and investigated these polymorphisms in drug resistant versus drug responsive patients.

Methods: DNA samples were obtained from 60 patients aged 2 to 18 years (mean: 9.28+4.96) with drug responsive epilepsy, 59 patients with drug resistant epilepsy aged 2 to 16 years (mean: 6.68+4.21) and 76 healthy subjects. CYP2D6*3 and CYP2D6*4 polymorphisms were

determined by polymerase chain reaction followed by melting curve analysis. Results were expressed as genotype and allele frequencies per drug responsive, drug resistant and control subjects and compared by X2 -test.

Results: Allele distributions of CYP2D6*3 and CYP2D6*4 were similar among the study groups. Genotype distrubution were also found to be similar among the groups. We could not demonstrate any statistically significant relation with CYP2D6*3 and *4 genotype in drug resistant patients. We also did not observe any significant correlation between the presence of a specific allele frequency and drug resistance.

Conclusions: The present study reports the first study of polymorphisms of CYP2D6 gene in intractable epilepsy, which demonstrates that the intractable epilepsy does not possess any association with CYP2D6 genotype and alleles.

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REVERSIBLE VISUAL CHANGES AND ELECTRORETINOGRAM (ERG) CHANGES IN A CHILD ON VIGABATRIN FOR INFANTILE SPASMS

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Rationale: This case report is important because this child had reversible visual symptoms, visual fields and ERG changes while on Vigabatrin. The current FDA Black Box warning states that irreversible peripheral visual loss and ERG changes may occur with this drug.

Methods: Pediatric neurology patients with infantile spasms on the drug Vigabatrin were examined by a neuro-ophthalmologist. Data on each child varied over the years as the children grew older and were able to cooperate. Visual acuities, pupil exams, motility exams, retinal exams, visual fields by Goldmann kinetic and Humphrey static techniques, ERG testing, OCT (optical coherence tomography)imaging and MRI imaging were all collected on this child.

Results: This child had infantile spasms starting at the age of 1 month in 2003. Two drugs failed to help, but at 6 months, Vigabatrin stopped his seizures by day 5. Baseline vision exams, ERG testing and CT of the brain were normal. At 18 months of age, still on Vigabatrin, he became both photophobic and afraid of the dark. Visual acuities were 20/60 OD and 20/40 OS estimated by fixation targets. Visual fields became constricted with a right homonymous inferior quadrantanopsia. ERG testing became abnormal at 18 months. The family chose to continue using the drug because of his clinical control on it. At age 41 months, his vision improved, visual fields expanded to normal (except for the right quadrantic defect) and ERG returned to normal while still on Vigabatrin. His seizures increased in frequency at 43 months and a left parietal cortical resection was done. Pathology showed cortical dysplasia. Genetic testing revealed the TSC2 genotype. Postoperatively, he was tapered off Vigabatrin over 10 months, and transitioned to Trileptal. At 7 years, he remains seizure-free on Trileptal and Rapamycin. His first Humphrey visual field tests showed the fixed right quadrantic defect (see image 1), and his first OCT testing of the macula showed a normal retinal thickness (image 2) after 4 years of Vigabatrin therapy.

Conclusions: Not all visual symptoms, visual field losses and ERG changes are irreversible with the drug Vigabatrin.

IMAGE: images/908160_A.jpg

Goldmann Visual Fields (above) and 1st Static Humphrey Visual Fields (below) in late 2009

IMAGE: images/908160_B.jpg

At age 7, his first OCT (optical coherence tomography) measurements of the maculas show good Retinal Thickness (there are no age-adjusted norms for this yet).

2.189

THE EFFECTS OF ANTIEPILEPTIC DRUGS ON RAT UTERINE IMPLANTATION

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Rationale: To determine (and compare) the effetcts of valproic acid (VPA), carbamazepin (CBZ), oxcarbazepine (OXC), levatiresetam (LEV), topiramat (TPM), lamotrijin (LTG) on uterine implantation of non-epileptic rats

Methods: Total of 147 rats, which had pregnancy 3 to 6 times before, were divided into three main groups (49 each). The subgroups were furher divided into 7 groups. For 30 days, while following the estrus cycles, six different antiepileptic drug were applied by gavage to different groups: VPA (300 mg/kg/day), CBZ (154 mg/kg/day); OXC (30mg/kg/day); LEV (50 mg/kg/day); TPM (100 mg/kg/day); LTG (10 mg/kg/day) and drinking water (for control). The drug applications were made in two doses. Following the drug applications, females were put together with male and vaginals smears were tested. The day vaginal plaque or sperm in vaginal area was observed, was accepted as the 0th day of implantation. On 5th day for the 1st main group, on the 7th day for the 2nd main group and on the 9th day of the 3rd main group the uterus including the embrios were taken out and the embryos were counted. The implanted embryos were immunohistochemically processed and laminin, kollajen IV and vimentin were investigated

Results: Although statistically insignificant, in groups received VPA, CBZ and OXC, the number of embryos were reduced ($p>0.05$). In the same experimental groups emryonic trofoblast cells and lumen epithelial cells of the uteruses exhibited weaker stainging intensities ($p<0.05$). For analysis Standard HSCORE =" Pi (i+1) was used

Conclusions: Antiepileptic drugs especially VPA, CBZ ve OXC may reduce the number of embryos and campared to LEV, TPM and LTG, have stronger negative effects on rat uterus implantation. In humans too, VPA, CBZ and OXC might contribute to infertility and abortion risks

2.190

DISPOSITION AND ADVERSE EFFECTS OF INTRAVENOUS TOPIRAMATE IN ADULT PATIENTS WITH EPILEPSY OR MIGRAINE HEADACHES

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Rationale: Topiramate (TPM) is a widely prescribed antiepileptic drug. An investigational intravenous (IV) formulation of TPM solubilzed in a cyclodextrin matrix, Captisol®, is being developed with the long-term goal of evaluating its safety and efficacy in neonatal seizures. However, pharmacokinetics (PK) and safety must first be demonstrated in adults. The aims of this study were to determine the safety and PK of TPM under steady-state condition in adult patients on maintenance therapy.

Methods: Twenty patients with epilepsy or migraine headaches completed the study. All patients were on stable, maintenance TPM therapy. The study was conducted at the University of Minnesota General Clinical Research Center. On the day of the study, patients had a brief physical and neurological examination, an EKG, and a battery of lab tests. Patients were given 25 mgs of a stable-labeled (SL) IV TPM over 10 minutes followed by their usual oral TPM morning dose. Blood samples were taken just prior to IV TPM administration and serially for 96 hours after dosing. TPM and SL-TPM were measured using a validated LC-MS method. Concentration-time data was analyzed using a noncompartmental approach with WinNonlin 5.2.

Results: Preliminary PK analysis has been completed on all patients. The mean (± SD) bioavailability was 95 ± 26%, half-life was 29.3 ± 11.3 hours, distribution volume was 0.81 ± 0.26 L/Kg, and clearance was 1.95 ± 1.02 L/hr. Seven patients experienced one or more minor adverse events: nausea and vomiting, tingling around the lips, paresthesia in the arms and legs, and one case of a vasovagal response with IV catheter placement. Four patients with uncontrolled epilepsy experienced a typical seizure during the study. No changes in heart rate, blood pressure, EKG, or infusion site reactions were observed.

Conclusions: Our preliminary results provide previously unreported information about IV TPM disposition and adverse effects. The infusion of small doses over 10 minutes appears to be safe. Oral absorption is approximately 100%, indicating that patients could be given the same dose IV as they are taking orally. The steady-state TPM half life appears longer than previously reported, supporting once or twice daily administration. Lastly, the distribution volume of approximately 0.8 L/Kg with minimal variability permits calculation of IV loading doses to quickly, accurately, and safely attain targeted TPM concentrations. Results from this pilot study will inform the design of subsequent studies, including controlled clinical trials intended to determine the efficacy and safety of IV TPM for neonatal seizures.

This study was supported by a grant from the FDA Orphan Grants program-R01 FD003540-01. CyDex Pharmaceuticals and the Epilepsy Research Foundation provided grants that supported preparation of the IV TPM formulation.

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LACOSAMIDE DOES NOT ALTER BONE DENSITOMETRY PARAMETERS IN JUVENILE DOGS

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Rationale: Literature suggests that long-term use of antiepileptic drugs (AEDs) such as phenytoin, carbamazepine, sodium valproate or phenobarbital is associated with reduced bone density which may lead to an increased risk of osteoporotic fractures. Studies in growing and young adult animals treated with AEDs have been shown to be good predictors of the human situation and thus support the relevance of animal studies in identifying bone effects. In the present study, the potential effect of lacosamide (LCM), a new AED, on bone quality was assessed in juvenile dogs.

Methods: Dogs were treated by the oral route (gelatin capsules) for 33 weeks, and a subset of animals was allowed to recover for 4 weeks. The age of the dogs at start of treatment was 7-8 weeks, which corresponds to a 2-year old child. The dose levels were 0, 3, 10 and 25 mg/kg once daily and 25 mg/kg bid. Due to subsiding signs of toxicity, the 25 mg/kg dose (once daily and bid) was increased to 30 mg/kg from test week 2 onwards and to 35 mg/kg from test day 60 onwards. The right tibia and lumbar vertebrae L3-L4 were subjected to dual energy X-ray absorptiometry (DEXA). Bone mineral content, area and density were calculated by the pDEXA machine software. The analysis of the tibia consisted of four regions of interest: total tibia, proximal and distal 25% of the tibia and midshaft 50% of the tibia. The two lumbar vertebrae were analyzed as one region of interest.

Results: After 33 weeks of treatment with LCM up to 70 mg/kg/day (35 mg/kg bid), there were no treatment-related adverse effects on bone mineral content, area or density in either male or female dogs, at either the lumbar vertebrae or any of the 4 regions of interest in the tibia. There were also no treatment-related effects on serum calcium levels, alkaline phosphatase activity or on bone (femur) histopathology. The no observed adverse effect level (NOAEL) in this juvenile dog toxicity study was defined as 10 mg/kg/day based on clinical signs (including tonic convulsions and emesis) observed at 35 and 70 mg/kg/day.

Conclusions: LCM daily treatment of juvenile dogs for 33 weeks at doses up to 70 mg/kg/day did not alter bone mineral densitometry parameters. The exposure at this dose level corresponds to clinically relevant exposure levels. The favorable profile of LCM in this juvenile dog study assessing the potential for bone alteration may be one of many key factors to consider when choosing a long-term treatment for epilepsy.

2.192

BIOEQUIVALENCE OF RUFINAMIDE ORAL SUSPENSION FORMULATION AND THE MARKETED TABLET

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Rationale: Rufinamide is indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome, a form of epilepsy with onset in childhood. Rufinamide is currently available only as a tablet formulation which may be difficult for some patients to swallow. Thus, a liquid (suspension) formulation has been developed.

Methods: Three suspension formulations were produced using different homogenization speeds (1800, 2100 & 3000 rpm) and evaluated in a comparative bioavailability study alongside the tablet formulation. The study was an open-label, randomized, 4-sequence, 4-period crossover study comparing the rate and extent of systemic exposure of rufinamide as either a single 400 mg tablet or 10 mL (400 mg) of each of the 3 suspensions. Twenty-four healthy male or female volunteers were evaluated. ANCOVA was used to estimate differences between treatment means and associated 90% confidence intervals for ratios of log transformed rufinamide pharmacokinetic (PK) parameters AUC(0-72h), AUC(0-inf) and Cmax.

Results: Bioequivalence was clearly demonstrated for all 3 suspension formulations with the currently marketed 400 mg tablet. Furthermore, each of the 3 suspensions were shown to be bioequivalent to each other (see Table). The extent of systemic exposure observed for the suspension and tablet formulations in this study was comparable to that seen in other studies. Of the 24 randomized subjects, 21 completed the study. Two subjects discontinued the study due to a non-treatment related AE (UTI) and one for an administrative error. Treatment-emergent AEs were mild or moderate in severity, with headache being the most commonly reported (38%).

Conclusions: All 3 suspension formulations were bioequivalent to each other and to the currently marketed tablet formulation. Speed of homogenization appears to have no discernible effect on PK parameters within the range evaluated in this study (1800 to 3000 rpm). The safety profiles of rufinamide for the three suspension formulations and tablets formulation were comparable. Once approved for use, the suspension formulation may be used at the same doses as the currently marketed tablets and can offer a useful alternative for patients who have difficulty in swallowing tablets.

Statistical Analysis of PK parameters (PK population)

IMAGE: tables/883569_T1.jpg

2.193

THE ROLE OF PHENYTOIN IN THE ERA OF NEWER ANTI EPILEPTIC MEDICATIONS: AN INTERNET BASED INTERNATIONAL SURVEY OF NEUROLOGISTS AND EPILEPTOLOGISTS

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Rationale: Phenytoin (PHT) has been the most widely used medication to treat both partial and generalized seizures. The availability of an IV formulation was a major advance in the acute management of seizures. However, over the past twenty years, a variety of new compounds have been released with comparable efficacy, fewer adverse effects, and more predictable pharmacokinetic properties. We surveyed neurologists and epileptologists to determine current practice patterns relating to the use of PHT.

Methods: A survey instrument with 11 questions (Table I) was created using the website www.surveymonkey.com. A link to the website was emailed to all members of the American Epilepsy Society (AES) in the Society's fortnightly newsletter on two successive occasions. In addition, using the online AES membership roster, all clinical members of the society were individually emailed a link to the survey.

Results: A total of 198 responses were obtained. Of the respondents, 78.1% were epilepsy specialists; 60% were adult practitioners, the remainder saw either only children or both adults and children. Four-fifth of the respondents practiced in the US. Almost all the respondents reported managing intractable epilepsy with the majority seeing between 20 and 40 patients per week. Only 2 respondents reported initiating more than 5 patients on PHT on a weekly basis. For new onset partial seizures only 10 respondents said PHT would be their first or second choice, while 45% reported that they would not consider PHT. Of all adult practitioners, 58% would use PHT among their first four choices for therapy of partial onset seizures as compared to 43% of pediatric specialists; the difference was non significant (p=0.1). However, every respondent felt that the drug was either very effective or somewhat effective in controlling seizures.

Conclusions: In this internet based survey of epileptologists and neurologists, we have demonstrated that while respondents felt that PHT was effective in the treatment of epilepsy, most would not recommend this medication as the first or second choice for the treatment of partial seizures. This study shows that in the era of newer medications, the role of PHT has been placed in the category of a reserve medication in intractable epilepsy.

Questions

IMAGE: tables/903388_T1.jpg

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USE OF LACOSAMIDE IN NONCONVULSIVE SEIZURES IN CRITICALLY ILL PATIENTS

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Rationale: Lacosamide(LCM) is a new antiepileptic drug approved as adjunctive therapy for partial-onset seizures. To date there have been two case reports of use of LCM for successful treatment of status epilepticus. The purpose of this study was to determine the efficacy of LCM in treatment of frequent nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) in critically ill patients.

Methods: Charts of patients with seizures determined by long-term electroencephalographic (EEG) monitoring were reviewed. Patients who received LCM for acute therapy were reviewed in detail. The patients were considered to be responders if their seizures were terminated with in 24 hrs of initiation of LCM without the addition of an additional antiepileptic agent. Characteristics of subjects whose seizures or NCSE was terminated with LCM were compared to those for whom this drug was not successful. In particular, the etiology, prior use of AED, as well as final outcome was noted. The dosing pattern of LCM, final dosage and adverse effects were recorded as well.

Results: A total of 32 patients received LCM for treatment of seizures or history of epilepsy. Of these, 15 patients received LCM for treatment of NCS or NCSE; 9 (60%) of them were responders. LCM was administered in the intravenous form in all except one patient and was administered as the 3rd to 5th agent. The average initial loading dose and total daily dose of LCM was similar in the responders and non responders (311 mg vs. 300 mg). All of the responders were noted to have NCS, while 33% of non responders had NCSE. Duration of seizures was 6.8 hrs for responders vs. 23 hrs for non responders. Etiology was related to primary brain tumor in 5 of the 9 (55%)

responders as compared to 1 of the 6 (16%) non responders. The responders were noted to have better clinical outcome (66% vs. 16% discharged home). Most of the patients tolerated the medication without any significant short term adverse effects; one patient was noted to be more aggressive following the addition of LCM.

Conclusions: Parental lacosamide appears to be efficacious as add-on for treatment of nonconvulsive seizures and status epilepticus in critically ill patients.

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TREATMENT OF MALIGNANT MIGRATING PARTIAL SEIZURES OF INFANCY WITH RUFINAMIDE: REPORT OF 5 CASES

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Rationale: The syndrome of malignant migrating partial seizures of infancy (MMPEI) (Coppola et al, 2009), is characterized by early onset of multiple seizures types emanating from different brain location across time, highly pharmaco-resistant seizures, and overall poor prognosis. The aim of this study was to describe our experience with rufinamide (RUF), a new anticonvulsant FDA-approved for add-on therapy in Lennox-Gastaut syndrome, in the treatment of MMPEI.

Methods: We undertook a retrospective analysis of charts of 5 infants with MMPEI who were treated with RUF. Records were analyzed for seizure types and frequency, EEG features, anticonvulsants used, and follow-up.

Results: Two of the 5 cases (case #1 and 2) had a dramatic response to RUF with a >50% reduction in seizure frequency. Case #1. A 26 month-old boy developed seizures since age 2 weeks. Semiology included clonic and/or tonic jerks of one limb, twitches of the eyelids, and chewing movements, along with desaturations and short apneas. Multiple EEGs showed electro-clinical seizures from the right and left fronto-central and temporal areas, and inter-ictal right temporo-occipital discharges. Seizures occurred in 1-5 clusters about 1-2 times per week. RUF was added to levetiracetam and topiramate, escalated to a maximal dose of 600mg/day (60 mg/kg/day). After 4 months, there were rare brief seizures reported (1/month) without desaturations and apneas, with no side effects on RUF. Topiramate was successfully tapered with 3 months of subsequent follow-up. Case #2. A 25 month-old girl had seizures since age 2 months. Semiology included tonic movements with eye deviation to one side and apneas with desaturation. EEGs showed electro-clinical seizures from the right frontotemporal areas, and left temporoccipital areas. Seizure frequency was about 7-10 seizures per week. RUF was added to levetiracetam and lamotrigine, with a maximal dose of 800mg/day (75 mg/kg/day). After 6 months, seizure frequency was reduced to 2-3 brief seizures per week, with no apneas and desaturations and no side effects. In the third case (case #3, a 30 month-old boy) RUF was discontinued because of side effects (vomiting). In the other 2 cases (case #4 and #5, 30-month and 36 month-old boys), RUF did not provide benefit at doses >50 mg/kg/day.

Conclusions: These results showed good efficacy and tolerability of RUF in 2 of 5 cases with MMPEI. Although limited, these results provide hope for a novel therapeutic option in MMPEI. Additional experience will elucidate the validity of this new drug for therapy in this otherwise devastating syndrome.

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LONG-TERM USE OF VIGABATRIN IN ADULTS WITH EPILEPSY

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Rationale: Vigabatrin was approved by the US FDA in 2009 for the treatment of infantile spasms and as an adjunct for the treatment of adults with refractory complex partial seizures. However, this was in use as an anti-epileptic agent in Europe as early as the late 1980s. Vigabatrin is a selective irreversible inhibitor of GABA transaminase. Studies have reported that about a third of patients on vigabatrin will have a related peripheral visual field (VF) deficit, usually after years of treatment. This review was aimed at evaluating the tolerability and sustained efficacy of long-term vigabatrin use.

Methods: Twenty-one patients were found that had been taking vigabatrin for at least 2 years. Of these, records were available for 19 patients. Information was recorded regarding age of onset, type of seizures and epilepsy, duration of vigabatrin use, reason for discontinuation if relevant, and any information regarding vision, including physical examination, formal VF, and results of electroretinograms (ERG).

Results: Ten of 19 patients were women. The average age at seizure onset was 13 years. Eleven patients were prescribed vigabatrin for seven or more years. Average maximum daily dosage was 3 grams. Thirteen patients had localization-related epilepsy, 3 with vascular malformations and 3 with brain tumors. All patients had previously failed multiple anti-epileptic medications.

Twelve patients (63.2%) had discontinued vigabatrin. Of these, 4 stopped secondary to VF constriction and/or abnormality on ERG, all having been on it for at least 2.5 years; one had visual symptoms and 3 did not. Four patients were tapered off because they were seizure-free for years. One patient stopped vigabatrin due to irritability; and 3 stopped due to lack of efficacy. Two patients were still taking vigabatrin at the time of the last follow up visit and remained seizure-free for at least 6 years. Of the remaining 5 patients, 2 died from tumor progression or other non-seizure related cause; 1 died from possible SUDEP; 1 was in a persistent vegetative state after status epilepticus; and 1 was lost to follow up. Of the 13 (68.4%) patients who were developmentally normal with refractory localization-related epilepsy, 6 patients (46.2%) became seizure-free during some period for an average of 7.5 years.

Conclusions: Among our 19 patients who took vigabatrin for at least 2 years, four had evidence of VF constriction and/or changes on ERG, all after >2.5 years of treatment. Six patients experienced prolonged seizure freedom for an average of 7.5 years.

Unfortunately, this sample size was small and information was reviewed in a retrospective manner. Also, many patients were seen as early as the late 1980s to early 1990s, so there was some inconsistency in terms of how the visual system was evaluated. VF changes generally occurred very late and were mild. Despite the potential risks, vigabatrin is a useful adjunct for patients with medically refractory epilepsy,

including localization-related epilepsy, and sometimes leads to long-term seizure freedom.

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EFFICACY OF LACOSAMIDE AS ADJUNCTIVE THERAPY IN ADOLESCENTS WITH INTRACTABLE EPILEPSY: A CASE SERIES

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Rationale: Epilepsy that has proven intractable to multiple antiepileptic medications has a low probability of achieving reduction in seizure frequency with the addition of another drug. Promising results, however, have been obtained in adult epilepsy populations with Lacosamide as adjunctive therapy. To date, there is no pediatric data published on the efficacy of Lacosamide. We report 8 adolescent patients with intractable epilepsy treated with Lacosamide as an adjunctive therapeutic agent.

Methods: Retrospective chart review was performed on the patients seen at Children's Hospital of Pittsburgh from 01/2009 to 04/2010 treated with Lacosamide. Data regarding demographics, seizure type, neurologic diagnoses, previous antiepileptic medications and other treatments used were collected and analyzed. Seizure frequency prior to and following treatment with Lacosamide was obtained by report of parent/primary caregiver.

Results: Eight patients, 4 males and 4 females, treated with Lacosamide were identified. Ages ranged from 11 to 18 years, mean age 15. Primary neurologic diagnoses included encephalitis, neonatal stroke, sequelae of prematurity, Aicardi syndrome, Tuberous Sclerosis Complex Type 1 and pervasive developmental delay with autistic features.

Seizure types included complex partial with and without secondary generalization, simple partial, atypical absence, tonic, and myoclonic. Various combinations of all antiepileptic medications available in the United States with the exception of felbamate and ethosuximide had either previously been used or were currently being given. Seven patients were using a vagal nerve stimulator prior to starting Lacosamide. Two patients had previously tried the ketogenic diet. One patient had a prior corpus callosotomy and the patient with Tuberous Sclerosis Complex had a prior right temporal lobectomy. Prior to starting Lacosamide all patients were having seizures no less frequently than once per week, with the majority having multiple seizures per week and 2 patients having daily events. Lacosamide doses used were between 100mg BID and 200mg BID, a range from 3 to 10 mg/kg/day by weight. 7 patients experienced an increase in total number of seizure free days by between 15 and 79% as reported by their parent/primary caregiver. One patient, prior to starting Lacosamide, had multiple daily complex partial and secondarily generalized seizures. After addition of Lacosamide the patient continued to have daily complex partial seizures, but the frequency of the secondarily generalized seizures decreased by 50%.

Conclusions: This case series illustrates that adjunctive treatment with Lacosamide may reduce seizure frequency in adolescents with epilepsy intractable not only to other antiepileptic medications but, to other treatment modalities as well, including VNS, ketogenic diet and surgery. Further study is warranted in the pediatric age groups.

2.198

ENTERIC-COATED, DELAYED-RELEASE DIVALPROEX WITH 1ST-ORDER ABSORPTION CHARACTERISTICS VS. EXTENDED-RELEASE DIVALPROEX WITH ZERO-ORDER ABSORPTION: GRAPHICAL COMPARISON AND VISUAL ANALYSIS OF PLASMA CONCENTRATION-TIME PROFILES

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Rationale: Most immediate-release and enteric-coated [EC] formulations of drugs, including AEDs, exhibit 1st-order absorption characteristics, with a constant fraction or % absorbed into the bloodstream per unit time upon oral administration. Certain AEDs have been engineered to markedly slow the rate of drug-release, ie., extended-release [ER] formulations, for purposes of minimizing peak-concentration-related toxicity. One such AED, divalproex extended-release, exhibits near zero-order absorption, with a constant amount of drug absorbed per unit time (Dutta, Reed, Cavanaugh, J Clin Pharmacol 2004; 44 [7]: 737-42; Dutta & Reed, J Clin Pharmacol 2006; 46 [8]: 952-7).

Plasma concentrations from multiple dosing of drugs with 1st order absorption characteristics has been commonly displayed graphically in various publications & general pharmacological texts; clinicians generally recognize this pattern of oral drug absorption (superposition principle). The pattern of plasma concentration rise with multiple dosing of ER formulations with zero-order absorption has not been depicted graphically and is not well-recognized. We graphically compared the absorptive phase of plasma concentrations for an AED, divalproex, with 1st order [EC] vs. zero-order [ER] absorption.

Methods: We simulated the total plasma concentration profiles of valproic acid [VPA] resulting from oral, multiple doses of two distinct divalproex formulations, EC vs ER, via parameters and formulas published previously (Reed RC & Dutta S, Am J Health-Syst Pharm 2004; 61 (21): 2284-9 and Reed RC, Dutta S & Liu W, Epilepsy Research, 2009; 87: 260-267). For divalproex EC, a ka = 0.091 (1/hr) was used; for ER, we used a k0 = 50.57 mg/h x 22 hr.

Results: Linear [VPA]-concentration-time profiles from EC (1st-order, pink) vs. ER (zero-order, blue line) with resultant [VPA] after missing a dose at h = 192, plus subsequent dose replacement, are shown in the figure. The pink EC [VPA] profile displays the classic superposition principle for drugs with 1st-order absorption, with a constant 'north-east pointing' vector, also clearly seen at steady-state and is again visually apparent with [VPA] post dose-replacement. The vector for the blue ER [VPA] profile is constantly changing, becoming flatter with each dose until a plateau is reached.

Conclusions: The graphical pattern of the rise in plasma [VPA] concentrations from oral multiple-dose divalproex-[EC] possessing 1st-order absorption is clearly different from that of divalproex-[ER] with zero-order absorption. It is important to recognize these patterns as more ER-AED formulations with zero-order absorption are likely to be developed.

IMAGE: images/913358_A.jpg

Linear pLot of 1st-order (eg., immediate-relaase AEDs) vs. zero-order absorption (certain extended-release AEDs)

2.199

RUFINAMIDE: EFFICACY AND SAFETY IN INTRACTABLE EPILEPSY (LENNOX GASTAUT SYNDROME AND NON LENNOX GASTAUT SYNDROMES) - OUR EXPERIENCE

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Rationale: Lennox Gastaut syndrome (LGS) is a severe form of childhood onset epilepsy that accounts for 1-4% of all childhood epilepsies. Seizures associated with LGS are often treatment resistant and children end up on multiple anticonvulsants. Rufinamide is an orally active triazole derivative antiepileptic drug (AED) that is structurally unrelated to other currently available AEDs. Its mode of action may relate to the modulation of sodium channel activity. Rufinamide has been approved as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults. Recent clinical trials suggest that the drug has efficacy for partial seizures. We conducted a review of the safety and efficacy of Rufinamide in the management of intractable epilepsy (LGS and Non-LGS) in children treated in our department.

Methods: Retrospective review of electronic case records of all children treated with rufinamide from 2007 -2010 in the department of neurology, Birmingham Children's Hospital, U.K supplemented by telephonic questionnaire to parents.

Results: A total of 34 children were identified (24 males and 10 females).

All children identified had intractable epilepsy .Seventeen (50%) had a diagnosis of LGS.

30 (84%) experienced multiple seizure types. 11 (32%) had >30 seizures /day while 13(38%) experienced <10 seizures/day. All of them had previously been trialled on 4- 17 anti epileptic medications with poor seizure control. Nine had been tried on ketogenic diet, 3 on VNS and 4 on both VNS and ketogenic diet. Majority of the children (27/34) were > 5 years old at start of Rufinamide therapy.

In the LGS group 7(41.2%) had achieved > 50% reduction in seizure frequency including 3(18%) who had complete seizure freedom for 2weeks- 4 months. In 1 child the benefit was sustained for only 4 months while in 2 it was sustained for over a year. 7(41.2%) experienced no change to their seizure frequency while in 3(17.6%) there was a worsening of seizures.

In the non-LGS group 3(17.6%) experienced a significant reduction in seizures while 11(64.7%) had no benefit and 3(17.6%) had worsening of seizure frequency.

11 (32%) children experienced side-effects on rufinamide mainly in the form of behavioural changes (6), vomiting (2) and others (constipation, loose stools and unusual sensations).

Thirteen children continued on Rufinamide after 1- 2.5 years of use while 1 child had to be weaned off after stabilisation. The drug was withdrawn in 12 because of lack of benefit, in 2 owing to significant side effects and in 6 because of worsening of seizures.

Conclusions: In a group of children with severe intractable epilepsy, Rufinamide, in our experience is both effective and safe to use. It is effective both in the in Lennox Gastaut syndrome and other intractable epilepsy syndromes. It was not possible to determine from this retrospective study if Rufinamide is particularly effective against any specific seizure type.

2.200

LEVETIRACETAM AND NEONATAL SEIZURES

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Rationale: Levetiracetam is a novel AED indicated for adjunctive treatment of partial seizures in patients greater than 4 years of age; however, a significant percentage of pediatric neurologists recommend levetiracetam as second, third, or subsequent agent for neonatal seizures. The purpose of this retrospective chart-review study is to review the epidemiological characteristics, etiologies, and risk factors and subsequent efficacy of treatment of neonates that were treated with levetiracetam in an NICU setting.

Methods: We performed a search for patients treated at the Texas Children's Hospital (TCH) Neonatal Intensive Care Unit (NICU) between Jan. 1, 2004 and Dec. 31, 2008. Their medical records were reviewed for age at treatment, gestational age, diagnoses, imaging and EEG findings, treatment with anti-epilepsy drugs (AEDs), and response to treatment.

Results: Our search identified 20 patients (14 female, 6 male) who were treated with levetiracetam in the TCH NICU between 2004 and 2008. Pediatric neurology was the prescribing service in all cases. Median age at diagnosis was 0.75 months (range .07-2.56 months). Most patients (n=14) were born at full-term; 3 were premature with gestational ages of 31-34 weeks. Patients had generalized (n=10), partial (n=5), or partial with secondary generalization (n=4); data was not available for 1 patient. Several patients had genetic or chromosomal abnormalities (n=7), including 2 cases of nonkeratotic hyperglycinemia. CNS infection was present in 6 cases, including CMV and HSV encephalitis. 2 patients had evidence of hypoxic injury to the brain. There were 12 patients with abnormal findings on MRI of the brain, including holoprosencephaly, small infarcts, and cortical dysplasias. EEG revealed focal seizure activity (n=9), generalized seizure activity (n=5), or no abnormalities (n=5). The patients were initially treated most often with phenobarbital (n=15). Levetiracetam was most commonly the 2nd or 3rd drug of choice (n=7, n=6 respectively) but also was the 1st (n=3), 4th (n=3), and 5th (n=1). It was used in conjunction with other AEDs including phenobarbital and fosphenytoin in 15 cases, and used as a single agent in 5 cases. Patients were treated to a median dose of 40 mg/kg/day (range 10-120 mg/kg/day). Seizure frequency improved in 10 cases, including 8 patients who were noted to be seizure-free during their hospital course. Two patients did not improve and had to be readmitted for seizure treatment. Seizure frequency was not recorded for 8 patients.

Conclusions: Our results demonstrate that levetiracetam may be used in conjunction with other AEDs to treat various classes of difficult-to-control seizures in the NICU. Our data suggest that there may be a reduction of seizure frequency with levetiracetam; however, more research is needed to evaluate its safety and efficacy in neonates.

2.201

SAFETY AND EFFICACY OF LACOSAMIDE IN CRITICALLY ILL PATIENTS

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Rationale: Seizure management is a significant issue in the care of critically ill patients. A significant proportion of patients in the intensive care unit (ICU) suffer from seizures which can directly impact morbidity and mortality. The clinician is challenged with choosing the safest and most efficacious method of seizure treatment. Although traditional anti-epileptic drugs (AEDs) are effective, they are often associated with adverse events and drug interactions. Lacosamide (LCM) is a new AED which is available in IV form and has not been shown to have any significant adverse effects or drug interactions. However, the safety and efficacy of lacosamide in critically ill patients has not been evaluated.

Methods: Critically ill patients in an ICU at Emory University Hospital who received LCM from April 1, 2009 to February 1, 2010 were retrospectively reviewed. Baseline demographic data, admission diagnosis, treatment indication, LCM dose and concurrent AEDs were recorded. Outcome measures were time to complete seizure cessation or 50% decrease in seizure frequency for patients being treated for status epilepticus or incidence of seizure recurrence for patients who received LCM for treatment of isolated seizures or following resolution of status epilepticus. Adverse reactions assessed included hypotension, hypoventilation, cardiac arrythmias, unexplained fever, elevated creatinine and elevated liver function tests (LFTs).

Results: 14 patients with 15 different admissions to the ICU were included in the study, with a mean age of 54.7 years. LCM was administered for treatment of ongoing status epilepticus in 7/15 patients and for either treatment of isolated seizures or following resolution of status epilepticus in the remaining 8. The most common loading dose of LCM was 200 mg while the most common maintenance dose was 400 mg/day. 14/15 patients continued to take LCM at discharge. 14/15 underwent continuous EEG monitoring for seizure detection. Complete seizure cessation was achieved in 3/7 of the patients that received LCM for treatment of status epilepticus while the other 4 patients experienced at least a 50% decrease in seizure frequency. 7/8 patients who received LCM for treatment of isolated seizures or following resolution of status epilepticus remained seizure free. LCM was the last adjunctive AED introduced in 13/15 patients. Within one hour of LCM administration, 2/15 experienced a decline in systolic blood pressure (>20 mm Hg) while one patient experienced a prolonged episode of bradycardia. One patient had elevation of liver function tests which led to discontinuation of LCM. No other adverse reactions were noted.

Conclusions: Lacosamide appears to be a safe and effective alternative for treatment of seizures in critically ill patients. Further studies are needed in larger series of patients to explore the correlation and clinical relevance of the episodes of hypotension, bradycardia and elevation in liver function tests that were seen in a very small minority of patients in our series.

Adverse Events

IMAGE: tables/893315_T1.jpg

Outcome

IMAGE: tables/893315_T2.jpg

2.202

EFFICACY OF A NEW ANTI-EPILEPTIC MEDICATION VIMPAT

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Rationale: To conduct a prospective study regarding the efficacy of a novel anti-epileptic medication Vimpat (Lacosamide). Vimpat was approved by FDA in 2009 as an adjunctive treatment option for partial onset seizures in patients 17 years of age and older. It is an anti-epileptic medication (AEM) with novel mechanism of action and presumably few side effects.

Methods: We are conducting a prospective review of 10 patients followed in our outpatient facility who were started on the new anti-epileptic drug Vimpat. All of the patients included in this study are adults with ages ranging from 20 to 61 years of age. The gender was exactly equally distributed between females and males. Of the 10 patients analyzed 50% suffered from complex partial seizures (CPS) with secondary generalization and 50% had CPS without generalization. Etiology of seizures was variable (including post encephalitis, post traumatic, vascular and heterotopias).

Results: The longest follow up so far has been 1 year. The rest of the patients have been followed for about 6 to 10 months. Among all patients, 60% reported improvement in seizure frequency, 10% reported worsening of seizure frequency (therefore Vimpat was discontinued), 20% reported no change in seizure frequency, and 10% could not tolerate the medication. Most patients (60%) did not report any side effects, 20% had only mild side effects that subsided shortly after initiation of therapy, and these included dizziness and itching. However, 1 (10%) patients developed severe skin reaction(itching) and stopped the medication, and 1 (10%) patient reported severe generalized weakness and intolerable muscle stiffness.

Conclusions: Epilepsy is a chronic neurological disorder affecting approximately three million people in the U.S. Only 47% will attain seizure control with their first AEM, and more than 30% will continue to experience seizures despite trying two or more AEMs. Vimpat (lacosamide) is a newly FDA approved antiepileptic medication for adjunctive treatment of partial onset seizures in people with epilepsy who are 17 years and older [American Epilepsy Society]. Vimpat's mechanism of action has been shown to involve the modulation of sodium channel activity in the nervous system. It is thought that Vimpat reduces sodium channel over-activity by prolonging the longer lasting resting state of the channel, a different action compared with current sodium channel blocking drugs. The most common adverse effects reported included diplopia, headache, dizziness and nausea. Our data indicated significant improvement in seizure frequency with the use of Vimpat. Although our study included limited number of patients, we can clearly establish improvement with the concomitant use of Vimpat and good tolerance of the medication. Further studies are necessary to be conducted with wider patient population to investigate the long term effect of Vimpat.

2.203

BONE DENSITY IN AMBULATORY EPILEPSY PATIENTS IN SOUTH FLORIDA

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Rationale: Bone density has been shown to be adversely affected by long-term use of hepatic enzyme-inducing antiepileptic drugs (EI-AEDs). We sought to evaluate bone density in a population of epilepsy patients in a sunny climate.

Methods: The lumbar spine and hip bone density of otherwise healthy adult ambulatory epilepsy patients with long-term epilepsy consecutively seen in an epilepsy clinic for uninsured patients were evaluated using the same DEXA machine. Statistics used were descriptive and partial correlations.

Results: Ninety-seven patients were evaluated; 64% were women, 87% were Hispanic and 85% were white. The mean age was 46 years (range 23-72) and mean age of epilepsy onset was 16 years (range 0-58). Sixty-two percent of patients had taken phenytoin for a mean of 19 years (range 1-62), 61% had taken carbamazepine for a mean of 17 years (range 1-41), 43% had taken phenobarbital for a mean of 15 years (range 1-41). No correlation with use of these EI-AEDs and bone density at any site, when adjusting for the effect of age, was found. Further, no correlation with the use of these EI-AEDS for more than 10 years, or with age greater than 50 years, and bone density at any site, when adjusting for the effect of age, was found. Increased age, but not gender, was the only variable associated with decreased bone density. One person reported a lifetime fracture, which was non-seizure related, in the upper extremity.

Conclusions: No discernable effect of EI-AEDs on bone density was found in this cross-sectional study. This may be due, in part, to a protective effect of the sunny climate in South Florida.

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RUFINAMIDE IN PEDIATRIC PATIENTS WITH LENNOX-GASTAUT SYNDROME AND NEURONAL MIGRATION DISORDERS

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Rationale: Rufinamide is a new antiepileptic agent that differs structurally from other antiepileptic drugs and is approved as adjunctive therapy for Lennox-Gastaut syndrome (LGS). It presumably provides its antiseizure activity by prolonging sodium channel inactivity, stabilizing cell membranes. It is absorbed and metabolized extensively, then excreted renally as an inactive metabolite. Clinical trials show that adjunctive rufinamide is effective at reducing seizure frequency in patients with LGS and refractory partial seizures. We evaluate the effects on seizures in 5 patients with lennox Gastaut syndrome secondary to neuronal migration disorders.

Methods: Materials and methods - In total, 5 patients (aged 4-17 years)with LGS and associate neuronal migration disorders (2 lissencephaly, 1 polymicrogyria, 1 bilateral periventricular nodular heterotopia, 1 tuberous sclerosis), receiving 1-3 concomitant antiepileptic drugs, were treated with rufinamide approximately 15-30 mg/kg/day. Efficacy was assessed by seizure frequency; tolerability by adverse events (AEs) and laboratory tests.

Results: Results All the patients showed reductions in seizure frequency throughout the study; during the last 6 months of treatment, 5/5 of patients had >/=50% reduction in total and tonic-atonic seizure frequency, respectively.

No side effeccts were noticed.

Conclusions: Data show that rufinamide is safe and effective as an adjunctive agent for LGS secondary to neuronal migration disorders. The benefits of rufinamide include its pharmacokinetics, limited drug interactions, and lack of side effects.

2.205

RUFINAMIDE IN FRONTAL LOBE EPILEPSY

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Rationale: Frontal lobe epilepsy(FLE) is a rare but challenging epilepsy syndrome . Carmabazepine and oxcarbazepine are considered the treatment of choice. About 30% cases of FLE prove to be resistant to medical treatment. We describe two children with refractory non-lesional FLE who became seizure free on rufinamide. Rufinamide, which was approved in 2008 by the FDA for treatment of Lennox Gastaut syndrome, is considered a broad spectrum anticonvulsant. However, its efficacy in frontal lobe epilepsy in children, has not been specifically reported

Methods: Two children, one 7 years old and one 6 years old, were diagnosed with frontal lobe epilepsy based on seizure semiology, ictal and interictal EEG. In case # 1 seizure semiology consisted of two weeks of escalating nocturnal episodes of sudden arousal, looking scared, and agitated behavior lasting 20 - 40 seconds. At presentation she was having 10 -15 episodes at night, as well as several episodes while awake, during the day. The initial EEG showed occasional bi-frontal sharp-waves. Ictal onset was with high voltage, bi-frontal rhythmic slowing. In case # 2 semiology consisted of a scared look, hyperkinetic leg movements, head retraction, turn to one side, hypertonia with tremoring , lasting upto 2 min. Initial nocturnal episodes were soon followed by diurnal ones.. Interictal EEG showed synchronous bifrontal spike and slow wave discharges. Ictal EEG had a generalized decrement with fast activity over bilateral frontotemporal regions at the onset followed by evolution in either hemisphere with frontal more than temporal involvement.Both children had normal brain MRI.

Results: In case#1, Initial treatment with oxcarbazepine , resulted in cessation of seizures within 4 days . Oxcarbazepine was stopped later due to rash . Seizures recurred on day two after stopping OXC. LEV was started. The rash resolved over the next two days but seizures escalated , occuring every 15 - 30 minutes. Topiramate was added with inadequate response. Valproic acid, phenytoin and pregabalin were used in succession with no effect. The child developed a rash again, this time temporally related to phenytoin. All anticonvulsants other than Topiramate were stopped and rufinamide was introduced.3 days after initiating treatment with rufinamide, the child became seizure free. In case 2- Oxcarbazepine controlled seizures but was stopped because of significant behavioral difficulty. Levatiracetam had no response.

Rufinamide was started with complete cessation of seizures and improvement of behavior.

Conclusions: We report 2 children with non-lesional FLE. Both responded to oxcarbazepine but a rash precluded its use in one and behavior difficulty in the other. Seizures were refractory to other anticonvulsants. Both became seizure free on Rufinamide. Although this is a report on just 2 patients , the results were dramatic. Rufinamide may be a viable treatment option for resistent FLE and could be considered early on in the treatment . This interesting observation needs to further validation.

2.206

ADJUNCTIVE TREATMENT WITH LACOSAMIDE: AN OPTION FOR GENERALIZED EPILEPSY ?

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Rationale: Lacosamide (LCM) was licensed in Germany for the treatment of focal epilepsy in September 2008. We investigated the efficacy and tolerability in 10 patients with idiopathic generalized epilepsy who failed at least 3 of 4 approved antiepileptic drugs (valproate, lamotrigine, topiramate, levetiracetam) and subsequently received LCM 100 - 300 mg/d as off-label adjunctive treatment. This is the first report on LCM exposure for more than six months in this group of patients.

Methods: Ten consecutive patients (6 females, 4 males, 20 - 62 years) were included. Syndrom diagnosis was based on seizure semiology, EEG findings and absence of structural lesions (5 cases of juvenile myoclonic epilepsy, 2 cases of grand-mal epilepsy and 3 cases of absence epilepsy). Previous treatment included valproate (all 10 patients), lamotrigine and levetiracetam in 9 patients and topiramate in 7 patients. All patients experienced at least 3 generalized tonic-clonic seizures (GTCS) within the 12-months period prior to LCM treatment (range 3 - 19 GTCS within 12 months). Efficacy was calculated comparing the seizure frequency on treatment with LCM to the 12 months before LCM treatment. Assessment of tolerability was obtained from patient reports and neurological examinations.

Results: Three patients stopped LCM due to side effects (tiredness, n=2) and lack of efficacy (n=2). The remaining seven patients have been treated with LCM add-on for 7 - 20 months so far. Two patients are seizure-free since starting LCM (for 16 and 20 months, respectively). Both patients experienced 12 GTCS during the 12 months before starting LCM. Three further patients showed > 75% and two patients > 50 % seizure reduction of GTCS. No increase in GTC seizure frequency was observed in any patient. One patient experienced an intermittent and self-limiting increase of generalized myoclonic seizures. No increase of absence seizures was reported. Tiredness was the most common side effect (4 of 10 patients). Concomitant AED medication was stepwise reduced according to the patients needs. Currently one patient is on LCM monotherapy treatment.

Conclusions: Lacosamide may be a good option for adjunctive treatment of generalized epilepsies. LCM is well tolerated in most patients. A randomized, double-blind, placebo-controlled trial should be established to further evaluate the potential of adjunctive LCM treatment in generalized epilepsies.

2.207

USE OF PREGABALIN IN NONCONVULSIVE SEIZURES IN CRITICALLY ILL PATIENTS

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Rationale: Pregabalin (PGB) has been approved for adjunctive therapy for treatment of patients with refractory seizures. To date there are no studies of use of PGB for treatment of status epilepticus. The purpose of this study was to determine the efficacy of PGB in treatment of frequent nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) in critically ill patients.

Methods: Charts of patients with seizures determined by long-term electroencephalographic (EEG) monitoring were reviewed. Patients who received PGB for acute therapy were reviewed in detail. The patients were considered to be responders if their seizures were terminated with in 24 hrs of initiation of PGB without the addition of an additional antiepileptic agent. Characteristics of subjects whose seizures or NCSE was terminated with PGB were compared to those for whom this drug was not successful. In particular, the etiology, prior use of AED, as well as final outcome was noted. The dosing pattern of PGB, final dosage and adverse effects were recorded as well.

Results: A total of 52 patients received PGB for treatment of seizures or for chronic pain. Of these, 22 patients received PGB for treatment of NCS or NCSE; 11 (50%) of them were responders. PGB was administered via the nasogastric tube or orally and was administered as the 3rd to 5th agent. All of the patients had received levetiracetam prior to addition of PGB. The average initial dose and total daily dose of PGB was similar in the responders and non responders (395 mg vs. 391 mg). A total of 18% of the responders were noted to have NCSE, while 55% of non responders had NCSE. Duration of seizures was 16 hours for responders vs. 35 hrs for non responders. Etiology was related to hypoxic brain injury in 4 of 11 (36%) of the non responders as compared to none (0) of the responders. The responders were noted to have better clinical outcome (64% vs. 9% discharged home). Most of the patients tolerated the medication without any significant short term adverse effects, except two patients who were noted to have dizziness and sedation.

Conclusions: Pregabalin appears to be efficacious as add-on for treatment of nonconvulsive seizures and status epilepticus in critically ill patients.

2.208

THE EFFECT OF VALPROIC ACID ON SERUM TOTAL CHOLESTEROL LEVEL IN CHILDREN WITH EPILEPSY

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Rationale: Weight gain is a well-known side effect of valproic acid (VPA), which is associated with change of serum total cholesterol (TC) level. However, there are controversies on the correlation between VPA and serum TC. This investigation was undertaken to evaluate the change of TC level in children with epilepsy on long-term VPA monotherapy and the related factors.

Methods: Epileptic patients on VPA monotherapy for more one year were recruited at the Department of Pediatrics, Pusan National University Hospital. The body mass index (BMI) and TC of before and after VPA treatment were obtained from all patients. We also analyzed change of serum TC according to dosage of VPA, serum drug level and other clinical data such as gender, age at start of treatment, type of seizure, etiology of seizure, duration of VPA medication and BMI. which could affect change of serum TC level.

Results: Eighty two children (49 male and 33 female) were included in this study. Mean serum TC of pre- and post-VPA medication was 153.5±31.0 mg/dL and 158.1±30.2 mg/dL (P>0.05), respectively. There were no clinically significant change of serum TC level according to dosage of VPA, serum drug level and other clinical data such as gender, age at start of treatment, type of seizure, etiology of seizure, duration of VPA medication and BMI (P>0.05).

Conclusions: Our results suggest that long-term VPA medication does not affect serum TC, and overweight at pre-VPA medication is not a risk factor for serum TC change.

2.209

LACOSAMIDE IN BRAIN TUMOR PATIENTS WITH SEIZURE DISORDER

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Rationale: In patients with brain tumors the frequency of epilepsy varies between 30 and 70% and depends on the tumor type, with slowly growing tumors being the most epileptogenic. Lacosamide is a new AED that has a novel mechanism of action which involves selective enhancement of the slow inactivation of voltage-gated sodium channels. It was developed for adjunctive treatment of partial onset seizures in adults over 17 years of age.

Methods: A retrospective chart review was performed. Twenty six brain tumor patients from three institutions were analyzed for variables including: age, gender, dosing, seizure frequency at baseline and after initiation of treatment, number of AEDs prior to addition of lacosamide, tumor histology, and side effects.

Results: Patients included eight females and eighteen males with an average age of 44 years (range 22-70). Thirty-eight percent of patients had oligodendroglioma and 23% had glioblastoma. On average, patients were receiving two AEDs prior to the addition of lacosamide. Median dose of lacosamide was 200 mg daily (range 100 - 700 mg/day). Physicians reported improvement in seizure frequency in 42% of the patients, with seizure freedom in 23%. Lacosamide was used as monotherapy for two patients. Reported side effects included: headaches, dizziness, tremors, mood changes, somnolence, unsteady gait, fatigue, dyspnea, arthralgias, jaw pain and visual changes.

Conclusions: Although limited, the experience in brain tumor patients with refractory seizures reveals applicability of lacosamide as an add-on therapy and, in selected cases as monotherapy.

2.210

A KETOGENIC DIET REDUCES HIPPOCAMPAL LONG-TERM POTENTIATION IN FREELY BEHAVING ADULT RATS

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Rationale: Ketogenic (high fat, very low carbohydrate) diets (KD) can reduce epileptic seizures. Hypothesized anticonvulsant mechanisms of KD include (i) increased actions of inhibitory transmitters, modulators, and/or channels, and (ii) decreased excitability or levels of excitatory transmitters. Either of these consequences might not only reduce seizures but could also affect normal brain function and synaptic plasticity. Here, we characterize effects of a KD on adult hippocampal long-term potentiation (LTP), a widely-studied type of synaptic plasticity that is thought to be a potential cellular mechanism for learning and memory. To maintain the most normal physiological conditions possible we performed chronic in vivo recordings in freely behaving animals.

Methods: Adult male Sprague-Dawley rats were placed on a control or KD (Bioserv #3666) for two weeks (ad libitum) prior to any manipulation. Under anesthesia, rats underwent stereotaxic surgery to chronically-implant electrodes in the dentate gyrus of the hippocampus (recording) and the perforant path (stimulating). After implantation, one week of post-surgical recovery was allowed before recording, resulting in a total of three weeks on a control or KD. Recordings took place in quiet chambers in which rats were habituated and allowed to move freely. Input/output (I/O) curves were obtained using the population spike amplitude of field potentials recorded in the dentate gyrus. Using the I/O curves, the 50% maximum current level was selected for subsequent stimulation. After 15 minutes of stable baseline, a tetanization pattern consisting of 5 Hz theta burst stimulation was delivered to induce LTP of the perforant path-dentate gyrus synapse. LTP was quantified as the post-tetanization % change in the population spike amplitude relative baseline levels. Intermittent recordings continued for 48 h after LTP induction.

Results: Compared to adult male Sprague-Dawley rats fed a control diet, KD treatment for three weeks significantly diminished the magnitude of potentiation in the dentate gyrus. Decreased potentiation was recorded at almost all time points, including the first time point tested (1 min) and up to and including the last time point (48 h after LTP induction). No overt behavioral differences were observed.

Conclusions: Three weeks on a KD reduces the magnitude of LTP in the dentate gyrus of freely behaving adult rats. These initial results are contrary to recent published work showing no effect of a KD on LTP in vivo. Methodological differences could account for this discrepancy, and are important to resolve. Reduced potentiation in rats fed a KD is consistent with a general increase in inhibition (or decrease in excitation) and an increase in seizure threshold. It is important to determine whether the reduced LTP reported here in adult animals is also present in juveniles, as a KD is often prescribed to children with epilepsy. In addition, it is important to determine if a KD impacts normal learning and memory significantly, and if these effects are reversible (and within what time frame) upon return to a control diet.

2.211

CHARACTERISTICS AND CLINICAL AND ECONOMIC OUTCOMES IN MEDICAID PATIENTS RECEIVING VAGUS NERVE STIMULATION (VNS) THERAPY FOR THE TREATMENT OF REFRACTORY EPILEPSY

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Rationale: VNS implant is an adjunctive therapy to antiepileptic drugs (AEDs) in patients 12 years or older with refractory partial-onset seizures that are not controlled with medication alone. The purpose of this study is to evaluate the clinical and economic benefits associated with VNS therapy in patients with refractory epilepsy in a real-world setting.

Methods: A retrospective cohort study design will be applied, using data from 5 Medicaid State claims databases (01/97-06/09), including Florida, Iowa, Kansas, Missouri, and New Jersey. Patients receiving VNS, who had e”1 neurologist visit with a diagnosis of epilepsy (ICD-9 345.xx, 780.3, or 780.39), e”1 medical procedure claims for VNS implantation, e”1 AED dispensing, and e”6 months of pre- and post-VNS health plan continuous enrollment are included. The pre-index period spanned from the latest of the start of enrollment, first diagnosis for epilepsy, or a prescription filled for an AED until the first VNS implantation date (index date), while the post-index period spans from the index date until the earliest of the VNS removal, death, end of enrollment, or data end date. Patients’ observation period was divided into 90-day intervals (i.e. quarter) and outcomes were repeatedly measured at each quarter. Morbidity were measured by frequency of hospitalizations, hospital length of stay, emergency room visits, outpatient visits, neurologist visits, fractures, motor vehicle accident-related injuries, head injuries, and status epilepticus events. Univariate and multivariate Poisson regression models will be used to estimate the incidence rate ratios of the morbidity and mortality outcomes between the pre- and post- index period. Univariate and multivariate regression models were also used to estimate the healthcare cost difference (quarterly) between the pre- and post- index period. Proportion of days covered (PDC) will be used to compare AED adherence (PDC e”0.8 = adherent) between the pre- and post- index period. AED treatment persistence (discontinuation rates and treatment duration) will be reported for the post-index period.

Results: Of the 1,846 patients meeting the inclusion criteria, the mean age is 27.6 years and 51.2% are males. On average patients have about 29.5 and 28.4 months of eligibility in the pre- and post-index period, respectively. On average (± SD) patients use 3.2 (± 1.4) different AEDs during the pre-index period, and overall, 81.3% of the patients have e”1 episode of AED polytherapy. Mean Charlson Comorbidity Index (±SD) was 0.61 (± 1.05). Proportions of patients with psychiatric comorbidities were 27.8% (depression), 14.8% (anxiety disorders), and 8.7% (bipolar disorder). 86.3% patients used antimicrobial agents and 56.7% patients used antipsychotic drugs. The analyses for clinical and economic outcomes are in progress; results will be available for the conference presentation.

Conclusions: Based on a sample of over 1,800 VNS patients, the clinical and economic outcomes before vs. after VNS therapy will be presented.

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VAGUS NERVE STIMULATION ALLOWS REDUCTION OF POLYPHARMACY IN MEDICALLY REFRACTORY EPILEPSY: 10 YEAR OUTCOME

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Rationale: We are presenting a 10 year experience after implant with the Vagus Nerve Stimulator (VNS) in refractory epilepsy patients in a total population of 540 patients. 220 (40.7%) are mentally challenged. All patients initially were on polypharmacy (2-4 drugs). We asked the question: could VNS adjunctive therapy contribute sufficient efficacy to reduce polytherapy to improve seizure frequency in the normal (N) and mentally challenged (MC) population. Literature review for the device supports a 50-90% reduction of seizure frequency, decreased seizure severity and improvement in quality of life measures, alertness and memory. [Epilepsy & Behavior 2009 Oct; 16 (2 321-4) Epilepsy & Behavior 2001 Apr; 2 (2:129-134) Epilepsy & Behavior 2, 563-567 (2001)] Systematic drug reduction over time with continuation of individual patients on VNS long term has not been published. Reducing and tapering meds, eliminates drug interations, potential drug toxicity, lowers costs and helps cognition.

Methods: A retrospective review of 540 charts was conducted on all patients implanted at Epilepsy Institute of NC. 220 qualified as Mentally Challenged (MC) by psychological testing (IQ 20-70). Implantation began in 1997. Efficacy was evaluated by seizure frequency, reduction of meds, VNS settings, adverse events, desire to continue VNS with guardian and patient consent. Medications were reduced after VNS settings were optimized for each patient. Clinic visits were conducted on a protocol. Patients were not surgical canidates & met FDA criteria for VNS stimulation. Polypharmacy taper was addressed after VNS threshold for that patient was reached (Approximately 1 Year). Educational meetings facilitated the process. We evaluated patients at years 1,2 and 6 for reduction of seizures. Efficacy is defined by percent seizure reduction after implantation. All drugs were kept in place until VNS was maximized.

Results: From 1997-2007 we reviewed 540 charts retrospectivly. 220 mentally challenged having IQs of 20-70 ages 12-66 years. 52% reside in a residential facility, IQs 20-30. 48% have IQs of 50-70 and these patients lived in communities and came to our office. The remaining 320 patients have IQs of 80-120, age range 15-65 years & live with their family. The reduction of seizure frequency group N-year 1 68%/group MC 59%. Year 2 group N 70%/group MC 60%. Year 6 no significant change from year 2. Seizure reduction is based on baseline seizure frequency. 10% of MC group and 5% of N group could not be tapered off polypharmacy and suffered multiple relaspes. Most patients who were on 4 drugs and VNS at study entry are now on 2 drugs and VNS. Patients who were on 2 drugs and VNS are now on 1 drug and VNS. The study is ongoing. 20 patients relapsed and went to the ED. 80% were in the MC group.

Conclusions: Both groups successfully tapered polypharmacy with support of VNS. Both groups had a similar response to VNS in seizure reduction. MC have more seizure clusters with relapses during the taper period. VNS facilitates polypharmacy reduction.

2.213

DOES MODAFINIL EXACERBATE SEIZURES IN EPILEPSY?

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Rationale: Fatigue is a strong predictor of cognitive dysfunction and quality of life in epilepsy. There are concerns regarding increased seizure risk with the use of stimulants such as modafinil. We examined whether addition of modafinil caused exacerbation of seizures in patients with epilepsy.

Methods: A centralized clinical registry was queried to identify patients who had a diagnosis code of epilepsy (345) and who were taking modafinil during a 10 year period (January 1999-August 2009). The records were examined to determine the etiology of the seizure disorder, antiepileptic drug use, indication and dose for modafinil, whether there was clinical or electrographic evidence of seizure exacerbation, and reason for discontinuation of modafinil. We compared patients with epilepsy without another underlying neurological disease to patients where seizures were secondary to a brain lesion.

Results: A total of 262 patients were reviewed. Of these, 106 did not have evidence of seizures or modafinil use; 156 patients were included for analysis. EEGs were available in 113 patients; epileptiform discharges were seen in 34. Sixty-eight patients had seizures while on modafinil but in all but 4, it was not felt that modafinil contributed to an exacerbation. In another 3 patients, seizures occurred only after modafinil was started, but in 2 of them, modafinil had been discontinued prior to seizure onset. The most common reasons for discontinuation included death due to reasons unrelated to modafinil use (12), no longer needed (9), psychiatric side effects (5), suspected medical complications (5), and ineffectiveness (3), though the exact reason could not be determined from medical records in a large number (43). The most common etiology for underlying seizures was brain tumor (33).

Twenty-three patients had epilepsy without other symptomatic brain injury; they were younger (age 49.3 vs 53.2) and took a higher dose of modafinil (254.5 vs 202.9 mg/day), though not statistically significant. Two patients had undergone temporal lobectomy, and had recurrence of seizures. Eight patients were on monotherapy AED at the time modafinil was administered; 11 were on 2 or more AEDs, and 4 were not on AEDs because they did not have active seizures. Modafinil had been started in 9 patients because of clear medication induced fatigue, 8 because of fatigue not otherwise specified, and for other reasons (6). Eight patients experienced seizures while on modafinil (p=NS). Clinical exacerbation of seizures occurred in no patients. EEG was available after modafinil was started in 4 patients. Two patients showed less slowing as compared to EEGs obtained prior to modafinil.

Conclusions: Our results demonstrate that the use of modafinil is not associated with exacerbation of seizures over a wide variety of neurological conditions. This was also seen in patients with epilepsy not secondary to an underlying lesion. Addition of modafinil did not exacerbate their seizures even in patients who were on AED polytherapy. Modafinil appears to be safe, and may potentially be used in patients with epilepsy and fatigue.

2.214

SEVEN YEAR FOLLOW-UP IN PATIENTS WITH REFRACTORY EPILEPSY TREATED WITH MEDIAL TEMPORAL LOBE DEEP BRAIN STIMULATION

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Rationale: Deep brain stimulation (DBS) of different intracerebral targets as a treatment for refractory epilepsy is under investigation in several clinical trials. The purpose of the present study is to report on the extended follow-up of patients with MTL epilepsy who underwent chronic DBS in medial temporal lobe (MTL) structures.

Methods: 11 consecutive patients (8M) with refractory MTL CPS+/-SG underwent uni-or bilateral MTL DBS depending on seizure onset localisation as determined by invasive video-EEG monitoring. When unilateral MTL DBS failed to decrease seizures with >90% after at least 2 years of stimulation, a switch to bilateral MTL DBS was proposed.

Results: After a mean follow-up of 7 years (range: 52 -105 months), 3/11 patients are seizure free for >12 months. 3/11 patient have a >90 % reduction in seizure frequency; 3/11 patients have a reduction in seizure frequency of 50 %; 1/11 patient has a reduction in seizure frequency of 30-50%; one patient is a non-responder. The mean output current is 1.9V (range: 0-3.1). In 1 seizure free patient unilateral DBS was interrupted after 48 months due to seizure freedom with continued seizure control at maximum follow-up.

In all patients (4/11) with a focal unilateral ictal onset a >90% seizure frequency reduction is found. In 2/5 patients with a regional unilateral ictal onset, a >90% seizure frequency reduction is found. In all patients (2/11) with bilateral ictal onset a <50% seizure frequency reduction is found.

9 patients were initiated on unilateral MTL DBS. In 5/6 in whom DBS failed to decrease seizures with >90%, bilateral DBS was started resulting in improved seizure control in 2/5 patients and seizure freedom in 1/5.

None of the patients reported side effects. One patient had asymptomatic intracranial haemorrhages along the insertion of the deep brain electrodes. In one patient a cable revision was performed. In one patient bilateral DBS was switched to unilateral DBS due to acute seizure induction upon output increase trials. Mean number of AEDs before and after DBS is 3.

Conclusions: This open study with an extended long-term follow-up demonstrates maintained efficacy of DBS in MTL structures. In >50% of patients, a seizure frequency reduction of at least 90% is reached. 25% of patients become seizure free.

2.215

BRAIN OXYGENATION RESPONSES IN CONTROL AND TETANUS TOXIN TREATED RATS

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Rationale: Closed-loop responsive electrical brain stimulation is an emerging new therapy for the treatment of epilepsy. Seizure-prone states may be characterized by changes in tissue oxygenation (OXY), and changes in tissue OXY have been observed in response to spontaneous seizures and epileptiform discharges. If tissue OXY changes contribute to seizure generation, then interventions that alter tissue OXY may have therapeutic value. In this study, we characterized tissue OXY changes in response to a range of electrical stimulation that is used in epilepsy research and therapy in control and tetanus toxin (TX) treated rats.

Methods: Focal seizures were induced by injecting TX (50ng/0.5il) into the neocortex or dorsal hippocampus of adult male Sprague-Dawley rats (275-325g) anesthetized with isoflurane. Each rat was allowed to recover a minimum of two weeks. For tissue OXY experiments, control and TX rats were anesthetized with ketamine (80mg/kg) and xylazine (12mg/kg, IP) and placed in a stereotaxic. An oxygen-sensitive optical probe (Presens) was attached to a platinum-iridium electrode and lowered to the same coordinates used for the TX injection. OXY measurements were acquired continuously at 4 samples/sec from either the hippocampus or neocortex. High-frequency (HFS: 20, 60, 200Hz), and low-frequency (LFS: 1Hz) stimulations were tested. Symmetrical biphasic square wave pulses were used, and were 160isec/phase for HFS and 500msec/phase for LFS. Pulse amplitudes ranged from 0.1-0.6mA. Burst durations were 2sec for HFS and 10sec for LFS. Because voltage tended to increase with the duration of the LFS, additional voltage-controlled experiments were performed with LFS using long bursts (30-600sec) of low-voltage controlled (±1V) stimulation.

Results: Tissue OXY changes were observed for all stimulation frequencies, and response amplitude tended to increase with current amplitude. The typical response, especially at high amplitudes, was a transient oxygenation decrease lasting several seconds, followed by a prolonged increase lasting for tens of seconds. In some cases, the OXY baseline changed after stimulation. For HFS, 20 and 200Hz evoked a small initial decrease, followed by a much larger OXY increase, while 60Hz stimulation evoked a large initial decrease followed by an even larger increase. The response to LFS was qualitatively different. The late OXY increase was much larger than that of the HFSs and often resulted in a persistent increase in the oxygenation baseline. Further experiments with LFS in the TX rat revealed a transient decrease in EEG spiking after LFS, and a mitigating effect on the OXY decreases associated with spontaneous seizures.

Conclusions: The observation that changes in tissue OXY varied by stimulation frequency and intensity suggest that stimulation-induced changes in tissue OXY could contribute to the therapeutic effect of responsive stimulation. These observations also suggest that measurement of tissue OXY can be a useful tool for assessing neural responses to electrical stimulation. Funded by: NIST Advanced Technology Program Cooperative Grant No. 70NANB7H7001

IMAGE: images/907017_A.jpg

A. Dorsal hippocampal responses to 30sec bursts of 1Hz, 500ms/phase, square wave stimulation. B. Dorsal hippocampal responses to 2sec bursts of 20Hz, 160is/phase, square wave stimulation. C. Dorsal hippocampal responses to 2sec bursts of 60Hz 160is/phase, square wave stimulation. D. Dorsal hippocampal responses to 2sec bursts of 200Hz, 160is/phase, square wave stimulation.

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ADULT-ONSET RASMUSSEN ENCEPHALITIS TREATED USING TRANSCRANIAL ELECTRICAL STIMULATION

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Rationale: Rasmussen's encephalitis is a rare, chronic, progressive disease that typically appears in childhood. Today, the only effective therapy is a hemispherectomy; however, this procedure is associated with irreversible neurological deficits. Novel therapeutic approaches for this condition are, therefore, necessary. One candidate might undergo cathodal direct current transcranial electrical stimulation.

Methods: We describe a case of a patient with late-onset Rasmussen's encephalitis treated with transcranial electrical stimulation. The therapy was transferred by a disposable subdermal needle 12mm in length, and is 0.4mm diameter (27 gauge; cathode) and typical golden cup electrode (anode), delivered by Nicolet Endeavor CR (VIASYS Healthcare, USA) with a maximum safety output of 2 mA. The site for stimulation was determined by the EEG electrode 10-20 system based in a previous study. A constant current of 1 mA intensity was applied to the scalp (C3 (-/cathodal)/contralateral supraorbital area (+/anodal)) for 60 minutes in four sessions (0, 7, 30 and 60 days).

Results: A 30 year-old male with late-onset Rasmussen's encephalitis underwent a constant current transcranial electrical stimulation of 1 mA intensity for 60 minutes in four sessions (0, 7, 30 and 60 days). Any complications were observed during the therapy. In the follow up, 6 months later our patient becomes seizure free, improved alert state and global aphasia.

Conclusions: In the transcranial electrical stimulation, a weak constant electric current is injected into the brain via two large scalp electrodes. This weak current induces a change in membrane threshold (hyper or de-polarization) that results in focal changes of cortical excitability — increase or decrease depending on the electrode polarity—that lasts beyond the period of stimulation, modulating the cortical excitability in the human motor, prefrontal, and visual cortex. This is the first time that transcranial electrical stimulation has been used in serial sessions to treat Rasmussen's encephalitis and avoid or delay surgical treatment.

IMAGE: images/907152_A.jpg

Sequential MRI scans findings. MRI coronal images (A) T2-weighted images show an initial enlargement of the left temporal lobe, (B) Hyperintense in the white matter of left hemisphere. (C) MRI coronal images T1 with Gadolinium, shows swelling in the left hemisphere, does not enhance and (D) volume loss of the left temporal lobe and

perisylvian regions and frontal gyral enhance with postsurgical changes due to the biopsy of the left temporal and parietal lobes.

IMAGE: images/907152_B.jpg

Nuclear scans findings. 99mTc ECD SPECT (A) and SPECT/CT (B) shows hyperperfusion in left fronto-parietal regions and hypoperfusion in the left temporal lobe. C) 18F-FDG PET/CT shows hypermetabolism in the left fronto-parietal regions and hypometabolism in the left temporal lobe.

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EVALUATION OF INDUCED CURRENT NEAR THE LEAD ELECTRODES OF VAGUS NERVE STIMULATORS DUE TO TIME-VARYING GRADIENT MAGNETIC FIELDS DURING MRI

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Rationale: The focus of this work was in the area of gradient induced currents effects on the vagus nerve stimulator in MRI. VNS Therapy is used in the treatment of epilepsy while MRI is commonly used in the diagnosis and treatment of epilepsy. The strong gradient fields present in an MRI scanner can produce induced currents near the electrodes of the vagus nerve stimulator that could interfere with intended pulse generator signals or be of magnitude that introduces safety concerns for patients. It is therefore necessary to understand/quantify such induced currents near the electrodes of vagus nerve stimulator.

Methods: A 3T Siemens MR scanner was used for the experimental measurements using an Echo Planar Imaging (EPI) sequence. B-dot probe measurements were used to determine the location of maximum gradients fields within the bore. Measurements were made with the VNS device (n = 6) in worst case configurations within a saline phantom at the location of maximum gradient fields with the stimulation turned “off”. Measurements were also made with the VNS device in the “on” configuration to evaluate the effect of the gradients on the output. In addition, confirmatory numerical simulations using code based on the low frequency impedance method and virtual family models were performed. The VNS was modeled in representative clinical regions to determine the induced current levels near the electrodes for comparison to measurements of the device in the “off” case. The measured maximum gradient waveform was used to generate the incident magnetic field for the simulation code. The Fourier transform of the waveform revealed three major frequency components. Simulations were then performed at these three frequencies and linear superposition was used to find the maximum gradient-induced current level.

Results: A strength duration curve was established for the lowest VNS output (0.25 mA) for effective durations 10 µsec - 10 msec. Measurements of induced currents of all devices tested were found to be under this strength duration curve. Measurements demonstrated negligible effect on the VNS output when the stimulation remained “on”. Numerical simulations confirmed these low levels of induced currents for the “off” case. Figure 1 shows the normalized induced current densities and magnitudes for the required incident field. The top three diagrams in Figure 1 show the current density levels inside the complete virtual family boy model at the three simulation frequencies, while the bottom three diagrams show the induced current magnitudes near the lead electrodes. Table 1 provides the peak induced current values found for the adult male virtual family model. For all cases the MRI gradient induced current levels near the lead electrodes were very low.

Conclusions: Measurements in a 3T scanner using a saline-filled phantom with the VNS device in worst case configurations is supported by numerical modeling. Results of both indicate that maximum gradient induced currents are less than the lowest expected VNS output current.

IMAGE: images/903554_A.jpg

Induced current strength within human model at three different frequencies.

IMAGE: images/903554_B.jpg

Peak to peak induced current strength under various testing conditions.

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THE FUNCTIONAL NEUROPROTECTIVE EFFECTS OF THE KETOGENIC DIET VERSUS STANDARD ANTIEPILEPTIC DRUGS IN EPILEPTIC KCNA-NULL MICE

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Rationale: : Cognitive impairment is increasingly becoming recognized as a significant co-morbidity in patients with epilepsy. This widespread problem is believed to be secondary to the etiology, severity of the disease state, and/or chronic anti-epileptic drug (AED) treatment. The underlying mechanisms leading to AED-induced cognitive dysfunction remain unclear. In contrast, there is emerging clinical data to suggest that the ketogenic diet (KD) may ameliorate memory dysfunction in epilepsy patients. In the present study, we assessed the effects of the KD vs. standard AEDs on seizure frequency and learning/memory function in a developmental animal model of epilepsy.

Methods: Spontaneously epileptic Kcna1-null (KO) mice were generated using heterozygous breeding pairs. KD (Bio-serv F3666) and AEDs [carbamazepine (CBZ, 40mg/kg/day, mixed with methylcellulose [MC] as the vehicle), phenobarbital (PB, 30 mg/kg/day, mixed with saline)] were respectively administrated ad libitum and intraperitoneally for 2 weeks (all treatments began at postnatal day 21; KD n=6, SD n=5, CBZ n=4, MC n=4, PB n=4). Control groups of KO mice fed a standard diet (SD) were injected with either saline or methylcellulose alone. After 7-10 days of treatment, each animal underwent 72 hrs of continuous video-EEG monitoring. Long-term potentiation (LTP) was evoked in hippocampal slices acutely prepared from all treatment groups with either high frequency stimulation (HFS, 100 Hz, 1 sec) or theta-burst stimuli (TBS, consisting of 5 trains delivered at 0.2 Hz).

Results: SD-fed KO mice exhibited a mean daily tonic-clonic seizure frequency of 5.5 ± 0.8. No significant differences were found between KO/SD and KO/CBZ groups; in contrast, KO/KD and KO/PB groups exhibited significantly decreased seizure frequencies compared to both KO/SD and KO/CBZ cohorts ($p<0.01$). Intact hippocampal CA1 LTP responses were seen in wild-type (WT) mice fed a SD, in contrast to KO/SD animals where intrinsic impairment of LTP was observed. Interestingly, neither PB nor CBZ restored the intrinsically impaired LTP responses in KO mice. In contrast, KO/KD animals showed a prominent reversal of LTP dysfunction. Methylcellulose had no effect on LTP, but CBZ alone worsened LTP maintenance in WT mice. Remarkably, the synaptic protective effects of the KD were still observed after cessation of KD treatment.

Conclusions: Epileptic Kcna1-null mice demonstrate impaired synaptic plasticity, likely as a consequence of repeated seizure activity.

Unlike PB and CBZ, however, the KD induced functional neuroprotective effects in hippocampal slices both during and after the treatment phase. Collectively, our data indicate that the KD may indeed exert functional neuroprotective (and possibly, anti-epileptogenic) effects in hippocampus.

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KETOGENIC DIET FOR THE TREATMENT OF SEIZURES ASSOCIATED WITH HYPOTHALAMIC HAMARTOMAS

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Rationale: Hypothalamic hamartoma (HH) is a rare cause of epilepsy associated with medically refractory gelastic seizures, often associated with a progressive encephalopathy. While surgical intervention has led to seizure freedom in many patients, there are no broadly effective non-invasive treatments. We have performed 180 surgeries on 150 HH patients and have maintained a research database. We asked if those patients who had previously attempted the ketogenic diet (KD) noted clinical improvement. Furthermore, using fresh surgically-resected specimens, we asked whether ketone bodies might affect the spontaneous rhythmic firing of small HH neurons that have been implicated in a conceptual model of seizure genesis.

Methods: Patients who had previously attempted the KD were identified by querying our proprietary HH database. Patients were contacted by phone or e-mail and administered a standard questionnaire documenting KD treatment course, efficacy, and adverse effects. Electrophysiological methods were performed on HH slices (300 ìm) from 4 patients in a recording chamber infused with physiological saline (34 °C). Gramicidin (20 ìg/ml) perforated-patch microelectrode recordings were performed in small HH neurons under IR-DIC illumination.

Results: Six patients (2.7%) were identified for inclusion (3 males, mean age 12 years). Table 1 summarizes the results. Of the four patients who responded to the KD (i.e., at least 50% reduction in total seizure frequency), two had a strong reduction in multiple seizure types (including complex partial, simple partial and atonic seizures). Two patients reportedly improved in school and/or behavioral functioning. Only minor side-effects (weight loss and hypercholesterolemia) were experienced. In electrophysiological recordings, a ketone cocktail consisting of 1mM â-hydroxybutyric acid (BHB) and 1 mM acetoacetate (ACA) reduced the spontaneous firing in 5 out of 7 small HH neurons (see Figure 1). Slight suppression of rhythmic activity was seen in 3 out of 7 cells after application with the ketone cocktail, and full blockade of spontaneous firing was seen in 2 out of 7 cells. However, ketones did not affect the discharge pattern in 2 out of 7 cells.

Conclusions: The efficacy of KD for epilepsy associated with HH is previously unreported. Our study demonstrates that while only a small percentage of patients have attempted the diet, two-thirds of subjects reported a reduction in seizures - with one patient having such a favorable response that they declined surgical intervention with 14 years of follow-up. Our preliminary cellular electrophysiological observations suggest that ketones directly modulate the intrinsic firing of small HH neurons in a manner that fits with our conceptual model of seizure genesis. The present study-despite the small number of patients-may support the use of the KD as a therapeutic option in those patients who do not have access to surgical intervention, who are particularly hesitant to pursue surgery, or who are incompletely controlled following surgery.

IMAGE: tables/896092_T1.jpg

Abbreviations: CPS - complex partial seizures; SPS - simple partial seizures; SE - side effects; TR - Too restrictive; IE - ineffective

IMAGE: images/896092_A.jpg

Effect of ketones on the spontaneous firing of small HH neurons. (A) Representative tracing depicting the firing pattern of small HH neurons. Small HH neurons exhibited spontaneous rhythmic pacemaker-like neuronal activity. (B) In 2 out of 7 HH neurons, HH-induced spontaneous activity was fully suppressed by a cocktail of ketones (BHB + ACA, each 1 mM). Two vertical bars in the membrane trace indicate a skip of 5 min washout period. (C) Ketones slightly reduced the rhythmic activity in 3 out of 7 HH neurons. (D) No change of spontaneous firing occurred in 2 out of 7 HH neurons exposed to the ketone cocktail.

2.220

REDUCTION OF NEOCORTICAL NEURONAL FIRING BY THERAPEUTIC TRIGEMINAL NERVE STIMULATION

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Rationale: Trigeminal nerve stimulation has been shown to reduce seizure activity in both animal models and in humans. However, the mechanism by which this occurs is unknown. A fundamental question is: How do neurons in the somatosensory neocortex respond to the high frequency trigeminal stimulation that has been shown to be necessary for the anti-seizure effect?

Methods: In this study, we recorded from multiple single neurons simultaneously in the primary somatosensory cortex of awake rats using arrays of chronically implanted microwire electrodes. We also implanted a nerve cuff electrode on the infraorbital branch of the trigeminal nerve contralateral to the recording site. Unimodal pulses were provided to the infraorbital nerve with current values ranging from 1-9 mA and at frequencies of 1-100 Hz.

Results: Trigeminal nerve stimulation reduced the firing of single neurons in a frequency-dependent manner, with maximal firing reduction at frequencies of 62.5 Hz and above. This effect was not greatly dependent on stimulus intensity throughout the current range tested. Each pulse to the infraorbital nerve was followed by a short latency (approximately 7 ms) excitatory response, followed by a period of post-stimulus inhibition.

Conclusions: These results suggest that therapeutic levels of trigeminal nerve stimulation may exert their effect in part by suppressing neuronal firing using intrinsic cortical inhibitory mechanisms. These findings have implications for the use of trigeminal nerve stimulation as a treatment for epilepsy.

2.221

EFFECT OF EVEROLIMUS ON SEIZURE ACTIVITY IN PATIENTS WITH TUBEROUS SCLEROSIS (TS)

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Rationale: TS is characterized by hamartoma formation in multiple organ systems and disabling neurological disorders including epilepsy, mental retardation, and autism. Neurosurgical resection with its associated complications and comorbidities is the current standard treatment for intractable epilepsy associated with TS. Recently, an open-label, phase II trial (NCT00411619) of everolimus, an orally bioavailable selective mTOR inhibitor, demonstrated a significant reduction in both subependymal giant-cell astrocytoma (SEGA) and tuber volume and was well tolerated. Secondary endpoints included potential changes in seizure frequency in patients treated with everolimus.

Methods: Patients e"3 years of age with a definitive TS diagnosis and evidence of serial SEGA growth (on MRI) were treated with everolimus 3 mg/m^2/d orally (titrated to tolerability to achieve target trough concentrations of 5-15 ng/mL). The primary efficacy endpoint was change in SEGA volume from baseline to 6 months.

Results: Twenty-eight patients were enrolled; median duration of treatment was 21.5 months (range 4.7-34.4). After 6 months of treatment, 21 patients (75%) had e"30% reduction in primary SEGA volume. Based on caregiver observation, the proportion of patients with daily seizures was reduced from 7 of 26 patients (26.9%) at baseline to 2 of 25 patients (8.0%) at month 6 and 1 of 25 patients (4.0%) at month 12. Of 16 patients with uncontrolled epilepsy for whom video-electroencephalogram data were available, captured electroclinical and electrographic seizures were diminished at month 6 compared with baseline (average 2.75 vs. 6.30 per 24-hour period, respectively; p = 0.022); 9 patients had decreases in seizure frequency (across all types of seizure), 6 had no change (all were event-free at both time points), and 1 had an increase. Interictal epileptiform activity during the first 15 minutes of stage II sleep also was reduced compared with baseline (median change -20.0 [range, -227 to 201]). Of the 9 patients who experienced a reduction in seizure frequency, evaluation of antiepileptic drug concentrations in the blood demonstrated minimal variations between pre- and posttreatment despite adjustments in dosage. Changes in seizure frequency would therefore appear to be attributable to everolimus therapy.

Conclusions: Everolimus significantly reduced seizure frequency in patients with TS. Based on these findings, everolimus may be a viable alternative to surgical resection for the treatment of intractable epilepsy in patients with TS, and additional research is warranted.

2.222

THE KETOGENIC DIET INHIBITS THE MAMMALIAN TARGET OF RAPAMYCIN (MTOR) PATHWAY

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Rationale: The ketogenic diet (KD) is an effective treatment for pediatric epilepsy, and although it has been in use for nearly a century, its mechanisms of action remain poorly-understood. Unlike other treatments for epilepsy, there is evidence that the KD possesses antiepileptogenic as well as anticonvulsant properties. mTOR is a protein kinase that regulates numerous cellular functions including growth, proliferation, survival, and synaptic plasticity. mTOR is activated by PI3K/Akt signaling in the presence of nutrients and growth factors, and inhibited by AMPK in the setting of energy starvation. Dysregulated mTOR signaling has been implicated in epileptogenesis in models of genetic and acquired epilepsies including tuberous sclerosis complex (TSC) and kainic acid (KA)-induced status epilepticus (SE). Given the ability of mTOR to integrate nutrient and energy signals, we investigated the effects of the KD on mTOR pathway signaling in normal animals as well as rodent models of epilepsy.

Methods: Sprague Dawley rats were given ad libitum access to KD with 6:1 ratio of fat to carbohydrate + protein (F3666; Bioserv) or standard diet (SD) beginning at P21. For the KA model, rats were injected with 15mg/kg KA i.p. to induce SE, and started on KD or SD after resolution of SE. For TSC experiments, conditional GFAP *Tsc1* knockout mice (*Tsc1*^{GFAP}CKO) and littermate controls were weaned to KD or SD at P21. mTOR activity was assessed using western blot (WB) for phosphorylation of its downstream target S6 (pS6) compared to total ribosomal protein S6. Upstream signaling was evaluated by WB for phospho Akt (pAkt), total Akt, phospho AMPK (pAMPK), and total AMPK. Tissue was harvested for WB after two weeks of KD or SD in normal rat and TSC experiments, and 1, 7, or 21 days after SE in the KA model.

Results: In normal rats, KD reduced pS6 and pAkt in hippocampus (24% and 14%, respectively, $p<0.05$ for both) and liver (45% and 54%, $p<0.05$ for both), but not neocortex. KD increased pAMPK only in liver ($p<0.001$). *Tsc1*^{GFAP}CKO mice on SD had higher pS6 ($p<0.01$) and lower pAkt ($p<0.05$) than controls. KD decreased pS6 and pAkt in combined neocortex and hippocampus of control mice (22% and 19%, $p<0.05$ for both), but not *Tsc1*^{GFAP}CKO mice. There was no effect of KD on brain pAMPK in control or *Tsc1*^{GFAP}CKO mice. KA-induced SE increased hippocampal pS6 acutely and at 7 days, with return to baseline by 21 days, and KD blocked this elevation at 7 days.

Conclusions: KD inhibited mTOR activity in hippocampus and liver of normal rats, most likely via decreased Akt signaling in both regions, as well as increased AMPK signaling in liver. KD also inhibited mTOR in control mouse brain. In contrast, KD had no effect on mTOR hyperactivation in the TSC model, possibly due to an inability of KD to bypass the genetic inactivation of *Tsc1*. However, in the KA model, KD blocked the SE-induced mTOR activation. As pharmacological inhibition of mTOR by rapamycin prevents epilepsy in some models, these results suggest that the KD may also have antiepileptogenic actions via inhibition of the mTOR pathway.

2.223

CHILDREN ON THE KETOGENIC DIET COMBINED WITH ZONISAMIDE OR TOPIRAMATE, ARE THEY AT HIGHER RISK FOR ACIDOSIS?

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Rationale: Ketogenic diet is a well established effective anti-epileptic method, used for patients with pharmacologically intractable epilepsy.

One of its potential side effects is metabolic acidosis. Zonisamide and Topiramate are carbonic anhydrase inhibitors. Hence, they can also cause metabolic acidosis.

This is to study the risk of developing severe acidosis in children on the ketogenic diet for intractable seizures, taking Topiramate (TPM) and/or Zonisamide (ZNS) versus those taking other anti-epileptic drugs (AEDs).

Methods: This is a retrospective study over a four year period in a tertiary child neurology center. 72 patients (38 females and 34 males) on the ketogenic diet were studied. Age at initiation of diet is (0.16-17.9 years, mean age 5.56). Data on acidosis was collected from 56 patients. The results were divided into two groups. Group A: 26 patients receiving a carbonic anhydrase inhibiting AED, 19 of whom are taking TPM, 7 taking ZNS. Group B: with 30 patients on other AEDs. The Bicarbonate (HCO3-) levels of the two groups were analyzed at baseline, induction, three months and six months visits.

Results: In group A, HCO3- mean level is 18.83 (95% CI 17.92-19.74), whereas in group B, HCO3- mean level is 21.03 (95% CI 20.14-21.92). The difference between the two groups was statistically significant at baseline (p=0.001). However, there was no significant change in the HCO3- mean difference between the two groups over six months period (p=0.934).

Conclusions: Patients taking a carbonic anhydrase inhibiting AEDs, have a lower HCO3 at baseline. However adding a ketogenic diet, does not seem to increase that risk for acidosis, compared to other patients taking AEDs that do not inhibit carbonic anhydrase.

HCO3 mean levels in groups A and B over the study period

IMAGE: tables/907042_T1.jpg

2.224

THE RISK OF SEIZURE RECURRENCE IN CHILDREN WITH REFRACTORY EPILEPSY SEIZURE FREE ON THE KETOGENIC DIET

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Rationale: Seventy% of patients with epilepsy have their seizures easily controlled, but thirty% develop intractable epilepsy, seizures resistant to two or three antiepileptic medications (AEDs). Obtaining seizure control with more antiepileptic medications in this group is disappointingly small, only about 3-5%. Short-term outcome studies show greater success on the ketogenic diet (KD). However, long-term efficacy of the KD is not well defined. The aim of this study is to determine the success of maintaining seizure freedom long-term in children with intractable epilepsy on the KD.

Methods: The Institutional Review Board approved this retrospective chart review. Between 1/1/1994 and 6/31/2009, 410 patients started the KD at The Children's Hospital of Philadelphia. 276 charts were reviewed. Demographic information was collected. Seizure freedom was defined as having at least one month of seizure freedom at any point during KD treatment. The clinical course and risk factors for seizure relapse were assessed.

Statistical analysis included Kaplan Meier survival curves.

Results: Sixty-five patients of the 276 met our criteria for seizure freedom on the KD. Males comprised 57%. The median age of starting the KD was four years old (range 0.3-16 years old). Seventy seven% had failed e"4 AEDs prior to starting the diet. The majority of patients (69%) were having daily seizures. Abnormal brain MRIs were present in 52% with periventricular leukomalacia (23%) and dysplasias (20%) as the most common abnormalities. The time from KD initiation to seizure freedom ranged from 1-20 months (median 1.5 months). The median time to seizure recurrence was less than three months. The chance of remaining completely seizure free by 18 months was only 3%. Despite this small chance of sustained seizure freedom the seizure frequency in those who recurred was less than their baseline seizure frequency. Seventy-two% were categorized as early responders, patients who became seizure free within the first 3 months of KD initiation, and 28% were late responders, those who became seizure free after 3 months. Being a late responder was not a risk factor for seizure recurrence (hazard ratio = 1.08). Abnormal brain MRIs, age of seizure onset, e" 4 AED failures prior to the KD and weaning AEDs within 3 months of KD initiation were not statistically significant risk factors for seizure relapse. Twelve of the 65 children remained seizure free throughout KD treatment, which ranged from 0.6-6 years. At their last follow up appointment 53% of the patients were on fewer AED's than prior to the KD.

Conclusions: Based on this long-term analysis, the KD is a beneficial antiepileptic treatment for children with intractable epilepsy. The probability of remaining completely seizure free over the long term is low. However, the seizure frequency of those that recurred was far less than before the diet. The diet also allowed for a decrease in the total number of AEDs, which often have many side effects. No baseline clinical features were identified as risk factors for seizure recurrence on the KD.

2.225

LONG-TERM EFFICACY OF VAGAL NERVE STIMULATION THERAPY IN YOUNG CHILDREN WITH INTRACTABLE EPILEPSY

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Rationale: Vagus Nerve Stimulation (VNS) has been approved by FDA for treatment of intractable epilepsy in children over 12 years of age. However, it is often used in younger children with intractable seizures because few other therapeutic options currently exist. There is little data on the efficacy of VNS therapy in the pre-adolescent patient cohort.

The aim of our study was to assess the long-term efficacy of VNS therapy in young children. We hypothesized that their seizure reduction with VNS therapy would be at least as good as that reported for patients over 12 years of age in EO1-EO5 landmark trials.

Methods: We retrospectively reviewed medical records of intractable epilepsy patients who were under 12 years of age at the time of VNS implantation. We included all such patients who underwent VNS implantation surgery at the University of Chicago during the time period from 1/1/2002 to 5/19/2009 and who had a minimum of 6 months of follow-up after VNS implantation. Outcome was quantified as percent seizure decrease from baseline. Statistical analysis of the data was done to determine if any of the parameters significantly influenced the outcome.

Results: Out of 42 patients studied, 28 (66%) had at least 50% decrease in seizure frequency, one half of patients had 75% decrease in seizure frequency, and 3 (7%) became seizure-free. Most of seizure reduction was achieved within the first 6 months of VNS therapy. Of note, there was a trend for further improvement in seizure reduction over 5 years of follow-up. Aside from seizure reduction, 69% of patients reported lasting improvements in mood and alertness.

Complication rate was 4.7% and events included cough, gag, hypopnea and a delayed surgical site infection. Subgroup analysis showed that the following parameters did not significantly influence the outcome ($p>0.05$): age at VNS implantation, duration of epilepsy prior to VNS implantation, EEG focality, and etiology of epilepsy.

Conclusions: Vagus Nerve Stimulation is an important adjunctive therapy for pre-adolescent children with intractable epilepsy. The 66% VNS response rate of our patients compares favorably to the widely sited VNS response rate of 50% for older children and adults with intractable epilepsy. Moreover, our cohort demonstrated a lasting benefit of VNS therapy over five years, including seizure reduction and improvements in mood and alertness. Based on our data, VNS therapy in pre-adolescent children with intractable epilepsy is effective and safe. Larger scale studies are needed to evaluate potential predictors of greatest VNS response in this vulnerable group of children.

IMAGE: tables/850296_T1.jpg

2.226

KETOGENIC DIET EFFICACY IN THE TREATMENT OF INTRACTABLE INFANTILE SPASMS

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Rationale: The objective of this study is to determine the efficacy of the ketogenic diet in controlling infantile spasms after failing traditional anti-epileptic medication therapy

Methods: A retrospective chart review study of 8 patients with infantile spasms age 3 months to 3 years; 6 females and 2 males. Six patients had symptomatic infantile spasms, and the remaining two had cryptogenic infantile spasms. All patients continued to have infantile spasms with evidence of hypsarrhythmia on their electroencephalograms (EEGs) despite treatment with ACTH and/or vigabatrin. Patients were started on the ketogenic diet. Time intervals until cessation of infantile spasms, as well as resolution of hypsarrhytmia were studied using parent reports and EEGs when available. Also the incidence of side effects from the ketogenic diet was monitored. Quality of life improvement was charted based on the care giver's perspective.

Results: All eight patients included in this study failed to respond to ACTH and/or vigabatrin before going on the ketogenic diet. Seven patients (88%) achieved cessation of infantile spasms within 4-10 weeks (mean 6 weeks) after starting the ketogenic diet. Four of these seven patients had follow up EEGs within 4-8 weeks of starting the diet showing recovery of the hypsarrythmia pattern. One patient did not have any improvement and had to quit the diet after 6 months due to excessive vomiting. At the 3 months visit, care givers of 7 of the 8 patients reported overall improvement of quality of life.

Conclusions: The ketogenic diet is a safe and potentially effective method of treatment for patients with infantile spasms; especially those who did not respond to customary medication therapies. The low incidence of side effects, as well as the reported significant improvement of quality of life makes it very encouraging to use the ketogenic diet in pharmacologically resistant infantile spasms patients. This would also encourage a prospective randomized study, studying the use of Ketogenic diet versus ACTH, or Vigabatrin as a first line treatment for infantile spasms

2.227

URGENT KETOGENIC DIET INITIATION HELPS ACCOMPLISH DISCHARGE IN UNREMITTING SEIZURES

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Rationale: The ketogenic diet is typically initiated following a multidisciplinary clinic evaluation and preliminary parent education. This allows for parental consideration of the role and potential risks vs benefits of the diet, as well as psychological preparation for the commitment required. At our institution, an urgent initiation occurs when the patient is already an inpatient and cannot be discharged because of the severity of his/her seizure disorder. We describe 11 urgent ketogenic diet initiations.

Methods: We identified from the clinic database 11 instances of urgent diet initiation in 10 pediatric patients, ranging in age from 2 months-13 years at diet initiation. Epilepsy diagnoses included symptomatic epilepsy (6), Migrating Partial Epilepsy of Infancy (2), Lennox-Gastaut Syndrome (1), and Doose syndrome (1). None of the patients was in status epilepticus. Uncontrolled seizures (mean 15/day, range 5-70) was the primary indication in 9 patients. A tenth patient had PDH deficiency with seizure onset during the hospitalization.

Results: The patients were taking multiple antiepileptic drugs (AEDs) (mean 4.7, range 3-6). In all cases ketogenic formula or eggnog (in orally fed patients) was used to initiate the diet. Advancement to meals of solids occurred in patients that were medically able to take oral foods. At least one parent of each child received comprehensive ketogenic diet teaching.

Three initiated patients remained on the diet for d" 1 month. The reasons for diet discontinuation included financial constraint, hematuria, and visualization of a large gallstone. Eight patients were discharged on the diet (one patient on 2 separate occasions.) Duration of the diet in these patients ranged from 6 weeks to >3 years. Reasons for discontinuation were family concern for kidney stone risk, lack of efficacy, and food refusal. With concurrent correction of metabolic acidosis all patients tolerated the diet, and all patients demonstrated ketosis with ketonuria +/- betahydroxybutyrate of at least 4.5 mmol/L. Two patients discharged on the diet subsequently died from their underlying disorders (mitochondrial disease, and Down syndrome with aspiration pneumonia.)

One month following discharge, 5/8 patients had achieved a e"50% reduction in seizures. Two patients were seizure free. AEDs had been reduced in 6 patients. Average length of stay in patients that were discharged home on the diet was 62 days. In these patients, the average number of days to discharge was 15 days from the first day of diet initiation (range 4-27 days).

Conclusions: Urgent ketogenic diet initiation is feasible and may provide an effective additional therapeutic approach in acutely refractory epilepsy. However, urgent initiation may not allow adequate time for full evaluation of family/patient financial resources, attitude

towards the diet, expectations, acceptance of medical risks, education, and psychological adjustment.

2.228

CATHODAL TRANSCRANIAL DIRECT CURRENT STIMULATION SUPPRESSES PTZ-INDUCED SEIZURES IN RATS

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Rationale: Cathodal transcranial direct current stimulation (tDCS) is a noninvasive method for regional suppression of cortical excitability. Cathodal tDCS is well-tolerated, inexpensive, may be applied in minutes, and in limited studies appears to increase the seizure threshold. Yet the capacity of tDCS to suppress ongoing seizures, such as those of status epilepticus (SE), has not been tested. To evaluate a possible role for tDCS in the treatment of SE, we tested its anticonvulsive effect on high dose pentylenetetrazol (PTZ)-induced seizures in rats.

Methods: Restrained unanesthetized rats were injected intraperitoneally with PTZ (75 mg/kg) while monitored by continuous video-EEG. Following PTZ injection, and one minute after the first myoclonic jerk, 1 mA (n=9) or 0.1 mA (n=9) cathodal tDCS was applied for 20 minutes. A control group received sham tDCS. Rats were then monitored by video EEG for another 10 minutes after which time a second PTZ dose (20 mg/kg. Video EEG continued for another 15 minutes after the second PTZ dose.

Results: All groups had similar latencies to the first myoclonus and the first generalized tonic-clonic seizure (GTCS). However, the initial GTCS was significantly shorter in the 1 mA tDCS than in the sham group (21.4 secs vs. 32 secs; $p = 0.02$). 3/9 rats in the sham group died after the first PTZ injection and 1/9 died in each of the two stimulated groups. The second PTZ challenge induced a GTCS in 6/6 surviving sham rats, in 4/8 of the surviving rats in the 1 mA group and in 6/8 rats in the 0.1 mA group ($p < 0.001$). Compared to sham, latency to GTCS following second PTZ injection was longer in the 1 mA tDCS group ($p = 0.02$) and in the 0.1 mA ($p = 0.04$) groups. The second GTCS duration was also significantly shorter in the 1 mA group (32 secs) as compared to sham (59 secs; $p = 0.03$).

Conclusions: Cathodal tDCS, delivered during the acute ictal state, appears effective in suppressing seizures in the PTZ rat model. Given its favorable safety profile, these data suggest a possible role for tDCS in the treatment of ongoing seizures such as those of SE.

2.229

THE EFFICACY OF THE KETOGENIC DIET IN CORRELATION WITH BETA-HYDROXYBUTERATE LEVEL

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Rationale: To study whether the antiepileptic effect of the ketogenic diet has any correlation with the level of beta-hydroxybuterate achieved at different times.

Methods: This is a retrospective chart review study over a four year period in a tertiary child neurology center. 72 patients (38 females and 34 males) on the ketogenic diet were studied. Age at initiation of diet is (0.16- 17.9 years, mean age 5.56). Data was collected on seizure outcome and quality of life (QOL) after 3 months and 6 months of being on the diet. This data was analyzed for relationship with the levels of â-HOB at the same time intervals.

Results: After 3 months of being on the ketogenic diet, 23 out of 33 patients (70%) had >50% seizure reduction, 5 patients (15%) had <50% seizure reduction and the remaining 5 patients experienced no change. There was no statistical difference in the â-HOB values between the groups ($p=0.486$). At 6 months interval, 21 of 26 patients (81%) had >50% seizure reduction, whereas 5 patients had <50% seizure reduction. Again, â-HOB levels did not differ between the two groups ($p=0.239$).

QOL improved in 24 (72%) patients at 3 months. This did correlate with a significant difference of â-HOB levels ($p=0.329$). This finding was replicated at 6 months visit where 17 (66%) patients reported improvement of QOL versus 9 patients had no improvement; the difference of â-HOB values was insignificant ($p=0.672$).

Conclusions: In patients treated with the ketogenic diet, there is no correlation between seizure control or quality of life and serum levels of beta-hydroxybuterate.

2.230

WILL SEIZURES IMPROVE BY SWITCHING FROM THE MODIFIED ATKINS DIET TO THE TRADITIONAL KETOGENIC DIET?

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Rationale: The modified Atkins diet (MAD) is a less restrictive version of the traditional ketogenic diet (KD), both of which are used for intractable epilepsy. It has been previously reported that children can maintain seizure control when the KD is transitioned to the MAD over time. What is unknown, however, is the likelihood of additional seizure control from a switch from the MAD to the KD.

Methods: Retrospective information was obtained from 28 patients who made this dietary change from 4 different institutions in Denmark, Germany, South Korea, and the United States.

Results: Eighteen (64%) were female, the median age at seizure onset was 2.3 years (range: 0.1-15.0 years), and MAD onset 5.5 years (range: 2.2-19.0 years). Nine (32%) had >10% additional seizure reduction with the KD above the MAD, of which 5 became seizure-free. None of the 5 children who did not improve using the MAD later responded to the KD. There was an increased likelihood of improvement if the patient had myoclonic-astatic epilepsy compared to all other etiologies combined, 78% vs. 11%, $p=0.001$. Additionally, all five children who became seizure-free only after transitioning to the KD had myoclonic-astatic epilepsy. A trend towards greater likelihood of improvement if a

child was fasted at KD onset was identified, but it did not reach statistical significance (78% vs. 42%, p=0.09).

Conclusions: These results suggest the KD probably represents a "higher dose" of dietary therapy compared to the MAD, rather than unique diets. The switch from the MAD to the KD may particularly benefit those with myoclonic-astatic epilepsy.

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KETOGENIC DIET: CLINICAL PREDICTORS FOR SIGNIFICANT SEIZURE CONTROL

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Rationale: The ketogenic diet (KD) has been reported as an effective therapy in children with refractory epilepsy (RE). The classic KD is usually initiated with fasting, followed by a 4:1 KD ratio. Initiation of the KD without fasting and lower initiation ratios have been reported to be better tolerated in young infants. The purpose of this project was to identify prognostic factors that may influence the response to KD in children with RE.

Methods: A retrospective chart review was performed for all patients on KD. Exclusion criteria included patients discontinued from the KD due to severe side effects within a few days of starting diet. Seizure outcome was graded as follows: Class I: >90% seizure reduction, Class II: 50-90% reduction, Class III: 50-25% reduction, Class IV: no significant change or <25% seizure reduction or worsening seizures. Parameters studied included: gender, seizure type (partial vs. generalized), age at seizure onset, development status (mild/moderate/severe delay), seizure frequency at baseline, number of AED used before starting the KD, fasting vs. non fasting induction and ratio of KD used. Regression Analysis was performed at 3, 6, 9 and 12 months follow ups.

Results: 57 patients met inclusion criteria documentation. Ages ranged from 1.7 years to 26.8 years (mean 14.3 years) with a male to female ratio of 1:1.2. Mean seizures at baseline were 12.9/day. Generalized seizures were seen in a vast majority (89%) of the patients. Class I and II seizure outcome was reached in 35% and 21% of patients at 3 month interval and dropped to 26% and 5% at 12 months respectively. Patients with normal or mild development delays showed a class I improvement in 54% of patients at 3 months and 46% at 12 months follow up, while children with moderate and severe delays revealed Class I outcome in 30% at 3 months and declining to 20% at 12 months (NS). Regression analysis of data revealed that at the 3 mo follow up early seizure onset and female gender were associated with less efficacy (p 0.036 and 0.002 respectively). Lower effectiveness was also seen with low baseline seizure frequency and non-fasting induction (p 0.056 and 0.065). At 6 mo follow up, higher KD ratio at starting and fasting induction were associated with better outcome (p 0.031 and 0.040). However this difference was not sustained at 9 and 12 months follow-up. The other variables tested did not reveal significant influence on seizure outcome.

Conclusions: Our study confirms the effectiveness of KD in all children with RE. Moderate and severe developmental delay, young age of seizure onset, low baseline seizure count and female gender were associated with worse outcome while higher KD ratio and fasting induction were associated with improved seizure control up to 6 months follow up.

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DEEP BRAIN STIMULATION FOR DRAVET SYNDROME: A 10 YEAR FOLLOW-UP STUDY

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Rationale: To describe the effects of deep brain stimulation in two adults with Dravet syndrome (DS)

DS is a genetically determined severe epilepsy associated with cognitive decline and ataxia. Diagnosis in childhood has become easier after the isolation of the gene responsible for the majority of cases. Many patients previously diagnosed with "vaccination encephalopathy" have been demonstrated to have DS. Diagnosis during adulthood is still challenging. The many types of seizures seen in these patients are typically pharmacoresistant. Mortality during childhood is high, mainly due to status epilepticus or sudden unexpected death in epilepsy. Since the seizures are not amenable to resective surgery, deep brain stimulation (DBS) is a possible treatment in this group of patients.

Methods: Two adults with genetically proven Dravet syndrome were treated with thalamic DBS targeted to the anterior nucleus of the thalamus and followed for 10 years. No changes in medications were done in the first year after DBS implantation. Subsequent changes in DBS parameters and medications were made in order to obtain better seizure control.

Results: One patient with partial onset seizures received DBS at age 19 and showed a marked improvement in seizure control immediately after DBS insertion and stimulation. The other patient with generalized onset seizures received DBS at age 34 and did not show any immediate benefit. Gradual decline in seizure frequency was observed during the 10 year follow-up period. No side effects or changes in cognition were observed in either of the patients.

Conclusions: This is the first report of (short and) long term results in Dravet patients treated with thalamic DBS. We speculate that the results of DBS for epilepsy in patients with Dravet syndrome may be related to age at initiation of DBS treatment and seizure type.

IMAGE: images/907189_A.jpg

2.233

CONCURRENT BETAHYDROXYBUTYRATE AND GLUCOSE LEVELS IN CHILDREN RECEIVING KETOGENIC DIET THERAPY

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Rationale: RATIONALE: The energy composition of the classic ketogenic diet (KD) consists mainly of fat calories. Although the exact mechanism is unknown, the KD can be used to manage seizures in patients with epilepsy. Non-fasting serum glucose levels during KD therapy have been observed to be lower than with a regular diet. In the presence of limited glucose, ketones provide an alternative energy

source. Ketone levels can be measured in serum as betahydroxybutyrate (BHB). We sought to examine the relationship between BHB and glucose levels following initiation of the KD.

Methods: METHODS: We reviewed laboratory data of children who received 4:1 KD as primary treatment of epilepsy from 2000 to 2004. Non-fasting glucose levels were drawn prior to and at 1, 3 and 6 months after initiation of KD therapy. BHB levels were determined at 1, 3 and 6 months following the initiation of therapy. Seizure control was evaluated based on parental reports.

Results: RESULTS: Of the 40 patient charts that were reviewed, 19 contained sufficient data for analysis. The mean glucose level prior to KD initiation was 94mg%. The average (non-fasting) glucose levels at 1, 3 and 6 months on the KD were 68mg%, 67mg% and 68mg%, respectively. The mean BHB levels at 1, 3 and 6 months were 5.1mmol/L, 5.4mmol/L and 6.1mmol/L, respectively. Complete seizure control following initiation of the KD was achieved in 4/19 (21%) children. Mean non-fasting glucose levels prior to and at 1, 3 and 6 months after KD therapy in this cohort were 90mg%, 65mg%, 73mg% and 68mg%, respectively. BHB levels in seizure free patients on the KD were 5.6mmol/L, 6.5mmol/L and 6.4mmol/L at 1, 3 and 6 months, respectively. Improvement in seizure control (50-99%) on KD was noted in 12/19 (63%). Mean non-fasting glucose levels prior to and at 1, 3 and 6 months after KD therapy in this cohort were 88mg%, 67mg%, 68mg% and 68mg%, respectively. BHB levels in seizure improved patients on KD were 4.9mmol/L, 5.6mmol/L and 5.9mmol/L at 1, 3 and 6 months, respectively. Less than 50% improvement in seizure control with KD therapy was noted in 3/19 (16%). Average non-fasting glucose levels prior to and at 1 and 3 months after KD therapy in this cohort was 83mg%, 74mg%, and 66mg%, respectively. BHB levels in this cohort were 4.7mmol/L and 5.7mmol/L at 1 and 3 months, respectively.

Conclusions: CONCLUSIONS: Following initiation of KD therapy for management of epilepsy we observed an inverse relationship between non-fasting serum glucose and BHB levels. Successful management of epilepsy with KD does not appear to correlate with either serum glucose or BHB titers.

2.234

EFFECT OF ACTH AND CORTICOSTEROIDS IN PATIENTS WITH DOWN SYNDROME AND EPILEPTIC SPASMS: A CASE SERIES

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Rationale: Epileptic spasms is an age dependent type of epilepsy syndrome with significant impact on neurodevelopment. Treatment of epileptic spasms in patients with Down syndrome is challenging due to associated medical problems. So far there is no strong evidence to favor any specific antiepileptic medication in this subset of patients. Some are concerned about using ACTH (Adrenocorticotropic hormone) and corticosteroids in these patients because the potential risks may outweigh the benefits. We report 4 patients with Down syndrome and epileptic spasms treated with ACTH and corticosteroids.

Methods: We reviewed charts of four patients with Down syndrome and epileptic spasms seen at SUNY Downstate Medical Center and Kings County Hospital. Data regarding patient characteristics, seizure onset, seizure type, EEG findings, epilepsy syndrome, hospital course, antiepileptic medications used and their side effects were collected and analyzed.

Results: Four patients, 3 females and 1 male, with Down syndrome (Trisomy 21) and epileptic spasms were identified. Age of onset of spasms was between 6 and 16 months (Mean 10.5 months). Clinical spasms were confirmed by video EEG in all patients. EEG showed modified hypsarrhythmia in three patients and hypsarrhythmia in one patient. Alternative treatment with topiramate or valproic acid was tried prior to starting steroids in 2 patients with no significant benefit. Three patients received high dose (100 to 150 IU/m2/day) of ACTH for 1 to 2 weeks followed by tapering doses for total 6 to 10 weeks and one patient received oral prednisone (2mg/kg/day) for 2 weeks followed by tapering doses for next 4 weeks. Two patients who received ACTH had normalization of EEG with complete disappearance of clinical spasms confirmed by Video EEG within 1 to 2 weeks of treatment and remained seizure free 1 year after the treatment. One patient who received ACTH, showed improvement in EEG and transient disappearance of spasms but they recurred after 4 weeks with additional tonic seizures accompanied by generalized paroxysmal fast activity on EEG. The patient who received prednisone did not show any improvement. All patients developed irritability and cushingoid features, which resolved after stopping the therapy. One patient who received ACTH had severe infection requiring ICU admission within a week after the completion of treatment.

Conclusions: In our case series, ACTH appears to be effective in the treatment of epileptic spasms in a considerable proportion of patients with Down syndrome. But therapy with ACTH needs extra vigilance in these patients as they may be more prone for infections. Larger prospective studies are needed to determine the efficacy and side effects of ACTH for this specific group of patients.

2.235

VAGUS NERVE STIMULATION (VNS) THERAPY IN CHILDREN AND ADOLESCENT WITH REFRACTORY EPILEPSY

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Rationale: To analyze efficacy and safetiness data in children less than 18 years old with pharmacoresistan epilepsy treated with adjunctive Vagus Nerve Stimulation (VNS) in Venezuela

Methods: 43 patients 26M (60,5%) 17F (39,5%) were retrospectively evaluated between 2000 and 2008. Mean age: 13,04 +/- 4,35 (5- 17); 17 (39,5%) were d" 12 years. Mental retardation was observed in 36 patients (84%), and Autism was present in 6 subjects (14%). Age at epilepsy onset: 3,44 +/- 3,53 (0-12), Duration of epilepsy by the time of implant: 9,85 +/-4,06 (2-16,4 years) Time of follow up: 1,92+/-1,75 (0,5-8 years) Number of AED: 3 +/- 0,86 (2-5). Twenty eight patients had partial seizures and 15 had multiple types of seizures. Seizures were counted at baseline and after 6 months, 12 months and 24 months of VNS Therapy. VNS parameters: Output: 1,57 +/- 0,41 (0,25-3 mA), On time: 24,81 +/- 9,58 (7-30 sec), Off time: 3,6 +/-1,93 (0,3-5 min).

Results: Mean number of seizures Pre-VNS: 200.2 +/-241.9 (2-1200/month) Post-VNS: 62,47 +/- 98,9 (0,5-450/month). 76.7% of patients had a decrease of 50% in the frequency of seizure and 28% of subjects had a seizure reduction of more than 90%. Magnet effect YES: 30 (69.8%) NO: 13 (30.2%). More alert: 18 patients (41-8%). Side effects: 11.6%. Best response was observed in Symptomatic LGS.

Conclusions: 1-Median seizure reduction was 70% after 6 months.

2-Seizure reduction e" 50%: 76% and e" 90%: 28% after 6 months

2- Forty one (41%) of patients reported to be more alert post VNS therapy

3-Positive magnet effect was observed in 69% of cases.

4- Best response was observed in symptomatic LGS.

2.236

KETOGENIC DIET EXHIBITS ANTI-INFLAMMATORY PROPERTIES: INVOLVEMENT OF PPAR PATHWAYS?

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Rationale: Ketogenic diet (KD) is a high-fat low carbohydrate diet that exerts anticonvulsive properties. The underlying mechanisms of this diet remain unclear. PPAR activation by high fat component of KD has been suggested. PPAR pathway activation may lead to anti-inflammatory effects. Here, we try to assess the anti-inflammatory effect of KD using a model of LPS-induced fever in rats. We also explored inflammatory response and PPAR pathways in the studied groups.

Methods: Male Wistar rats (200-260 g) were housed 4 per cage on an alternating 12:12 light-dark cycle with day. Two groups are studied: Ketogenic diet group (n=8) that received KD during 14 days (Ketocal, SHS, Liverpool, UK) and control group (n=8) that received standard diet during 14 days. Both group received an i.p. injection of 50µg/kg of LPS. The body temperature was assessed each 15min during 4 hours. The temperature room was 20-22°C. Serum, liver and brain sample were analyzed in the two groups. The expression of both PPARá and PPARã were analyzed in the brain and the liver from additional animals (n=8 in each group).

Results: Hyperthermia induced by LPS appeared 2h after LPS injection in control group. The body temperature remains below 38.5°C at all time points in the KD group. A significant difference between the groups was observed from 2.5h after LPS injection to the end of the experiment (Figure). Looking at PPAR expression by PCR, we observed in the liver an increase of both PPARá and PPARã expression in the KD group while there was no significant difference in the brain. Cytokine profile is under investigation.

Conclusions: KD has anti-inflammatory properties. It is now well established that inflammation may contribute to seizure precipitation. The anti-inflammatory effect of KD may be involved in the anticonvulsive effect. PPAR pathways may be explained this anti-inflammatory properties.

IMAGE: images/907343_A.jpg

2.237

ADDING A KETOGENIC DIET TO VAGUS NERVE STIMULATION OR IMPLANTING VAGUS NERVE STIMULATOR IN PATIENTS RECEIVING A KETOGENIC DIET, DOES IT MAKE A DIFFERENCE IN SEIZURE CONTROL AND QUALITY OF LIFE?

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Rationale: Epilepsy is one of the most common pediatric neurological disorders. A fair percentage of patients will become pharmacologically intractable, requiring further non-pharmacological methods of treatment. Ketogenic diet and vagus nerve stimulation have been well studied, safe, wide spectrum anti-epileptic methods, with proven improvement in quality of life as well as seizure burden.

The objective of this study is to study the efficacy of combining a ketogenic diet, and vagus nerve stimulation, with either being initiated first in patients with pharmacologically intractable epilepsy.

Methods: A retrospective chart review study in a tertiary child neurology center studying 12 patients with pharmacologically intractable epilepsy, with different epilepsy types, who are receiving a ketogenic diet, as well as having vagus nerve stimulator implanted. There were 4 males, and 8 females. With age ranging between 2.25 and 17.9 years old. These patients were devided into two groups; Group A: are patients started first on a ketogenic diet, with some seizure improvement then vagus nerve stimulator was implanted later due to continuing seizures. Group B: are patients with a vagus nerve stimulator implanted first, with some seizure improvement, then a ketogenic diet was added later due to continuing seizures. Outcome for seizure control and quality of life was studied in each group at one month, three, six, twelve, and twenty four months.

Results: Out of the twelve patients, six were started on a ketogenic diet first (Group A), and six had a vagus nerve stimulator implanted first (Group B). In both groups, there was reported over 50% seizure reduction and quality of life improvement by 6 months of initiating the second treatment and that continues for long term. With no significant difference in the reported seizure control between both groups.

Conclusions: Both the ketogenic diet and vagus nerve stimulator are safe, effective anti-epileptic treatments. This study did not show a significant difference in seizure control between patients on a ketogenic diet, then have a vagus nerve stimulator implanted, compared to patients who have a vagus nerve stimulator implanted first then a ketogenic diet is started.

2.238

NICOTINE PATCH FOR THE TREATMENT OF INTRACTABLE ADNFLE IN A NON-SMOKING PEDIATRIC PATIENT

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Rationale: Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is an inherited seizure disorder characterized by mutations in the gene encoding the neuronal nicotinic acetylcholine receptor (nAChR).

Based on our review, there is only one case report on the use of nicotine to treat ADNFLE. Willoughby et al (2003) observed that smoking and nicotine exposure correlated with a decrease in seizures in one patient with ADNFLE and a longstanding smoking history. Brodtkorb & Picard (2006) found that tobacco use was associated with improved seizure control in 22 subjects with ADNFLE.

To our knowledge there have been no studies investigating the use of nicotine to treat ADNFLE in non-smoking pediatric patients.

Methods: We report a non-smoking 15 year-old African American female, with ADNFLE who responded to treatment with a nicotine patch. Seizures were refractory to numerous antiepileptic drugs, and refractory to right-frontal resection. Despite the use of medication and surgery, she continued to have at least 15 to 20 seizures per day, occurring during wakefulness and sleep.

We initiated treatment using one-half of a 7 mg nicotine patch (Nicoderm CQ 7 mg; GlaxoSmithKline, USA) for a two-week period, which resulted in no change in seizures. The patient remained on Keppra 2000mg BID, in combination with Prozac 20mg daily due to anxiety.

We increased to one 7 mg nicotine patch daily, for two weeks, which again resulted in no change in seizures. We discontinued the nicotine patch for a few months, and the patient continued to have at least 15 to 20 seizures per day. Vimpat 200mg BID was then added, and seizures decreased to 10 to 15 events per day.

We then pursued a trial with a 14 mg nicotine patch, in combination with her other medications, which resulted in an immediate response. Seizure frequency and duration decreased to one to two seizures per day, with seizures lasting one to four seconds. The patient and her family reported a profound improvement in seizure control and in overall quality of life.

Results: Seizures remained refractory to the use of half of a 7 mg nicotine patch and to one 7 mg patch. There was no response until the dose was increased to 14 mg, resulting in a distinct and profound improvement in seizure control. This significant response was noted immediately after starting the 14 mg patch.

Conclusions: This is the second case report using nicotine to treatment ADNFLE. However, this is the first case report on the use of nicotine in the treatment of intractable ADNFLE in a non-smoking, pediatric patient. In this N-of-one study, nicotine was clearly therapeutic for treatment of seizures, which has never been reported in an individual without a previous tobacco addiction. These novel findings suggest that nicotine may be beneficial for other pediatric and adult patients with ADNFLE, without a prior smoking history. This promising case report will ideally lead to future studies and ongoing research evaluating the use of nicotine in ADNFLE for patients of all ages. Additional studies are needed to further clarify effective dosing recommendations for transdermal nicotine.

2.239

SUCCESSFUL MAINTENANCE OF KETOSIS USING PARENTERAL NUTRITION THERAPY

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Rationale: The ketogenic diet is a well-established treatment for refractory epilepsy, but when enteral feeding is contraindicated, few data show whether a ketogenic total parenteral nutrition (TPN) is efficacious and safe. In 2 previous case reports, use of a highly ketogenic TPN (ratio 3:1 to 4:1) was associated with electrolyte disturbances and sepsis; it is unclear whether these complications were due to the TPN therapy or due to preexisting malnutrition. We report on the successful maintenance of ketosis using a lower ratio ketogenic TPN in a 34-month-old girl with seizure disorder of unknown etiology who required prolonged bowel rest.

Methods: The girl initiated the ketogenic diet at 20 months of age, and within 1 month, seizure frequency decreased from daily seizures with intermittent episodes of status epilepticus to 2 - 3 seizures per month using a 4:1 ketogenic ratio. In addition, she continued to require 4 antiepileptic drugs. She presented at 34 months of age with megacolon, pneumoperitoneum, and rectal bleeding requiring bowel rest, intubation and TPN. Given the severity of her epilepsy and efficacious response to ketosis, a ketogenic TPN was prescribed. TPN provided a mean daily energy of 40 kcal/kg/day (82% of estimated energy needs) from a 0.5% dextrose solution, with 2 g/kg/day protein, and a 20% lipid emulsion providing 2.5 - 4.0 g/kg/day of fat. During the 12 days of TPN therapy, ketogenic ratio ranged from 1:1 to 1.65:1.

Results: Ketosis was maintained as measured by plasma beta-hydroxybutyrate of 2.93 mmol/L on the 11th day of TPN. At a 1.65:1 ratio and 4.0 g/kg of fat on day 3 of TPN, patient's triglyceride level rose to 836 mg/dL. Due to the hypertriglyceridemia, the TPN was stopped for 24 hours, then restarted and increased slowly over 3 days to provide a final ratio of 1.3:1 and 3.0 g/kg/day of fat for the remaining period of bowel rest. Seizures requiring lorazepam and phenobarbital bolus occurred on days 8 and 9 of TPN. The patient's weight after the course of TPN was unchanged from her baseline weight.

Conclusions: When enteral feeding is contraindicated, a lower-ratio ketogenic TPN can be used to maintain ketosis and provide nutrition support.

2.240

LIFE-LONG REFRACTORY EPILEPSY CONTROLLED BY A NOVEL ACIDOSIS-SPARING, EUKETONEMIC KETOGENIC DIET: A CASE HISTORY

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Rationale: Drugs and other treatment options still leave a significant proportion of people with epilepsy with ongoing seizures. Can an acidosis-sparing euketonemic ketogenic diet (ASEK) better address many of the neurobiological factors that affect the likelihood of seizures occurring?

Methods: To describe the clinical history of a person with severe epilepsy and the novel dietary changes to her management leading to dramatic improvement in control of her seizures.

Results: RA is a 40 yr old female with subcortical band heterotopia. She had autism and seizures with multiple atypical and morphing seizure types which started when she was 9 months old. She was first hospitalized for status epilepticus (SE) at age 13 and was started on carbamazepine. Her seizures remained refractory on various AED combinations. She had 8 further admissions because of SE, the last SE and hospitalization occurring at age 33. RA started ketogenic dietary treatment at age 27. Her dietary management has evolved over a period of 13 years and she has had only occasional minor break-through

seizures in the last 7 years generally associated with viral infections. EEG at age 35 was essentially normal. Primary treatment consists of phenytoin maintained at maximum therapeutic level, high dose levetiracetam, and ketogenic-based diet formulated for: reduction of low-grade metabolic acidosis, caloric and nutritional sufficiency, and protection of mitochondrial and peroxisomal beta-oxidation pathways. RA's CO2 content is 25 Meq/L (normal 22-31), beta hydroxybutyrate is 0.33 mM/L (normal up to 0.3), and triglycerides 0.67 mM/L (normal <1.7). Ancillary treatment consists of managing hormonal and psychological stressors, constipation, and ensuring quality of sleep. RA is in excellent health, and shows cognitive and social rehabilitation indicative of recovery from autistic dysfunction.

Conclusions: This case history suggests the potential of a novel euketonemic diet to improve markedly seizure control and quality of life in people with refractory epilepsy. We are aware of a female aged 10 yrs and male aged 15 yrs with Lennox Gastaut syndrome, and a female 15 yrs with subcortical band heterotopia who have shown marked improvement in seizure control following ASEK principles.

2.241

EPILEPSY SURGERY FOR TEMPORAL LOBE EPILEPSY WITH MESIAL TEMPORAL SCLEROSIS: THE IMPACT OF MEASURING HEALTH-RELATED QUALITY OF LIFE AND PSYCHOSOCIAL OUTCOME

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Rationale: To evaluate long-term QOL in a homogenous group of patients with TLE due to mesial temporal sclerosis (MTS) and the impact of ATL on psychosocial function.

Methods: Eligible patients were those with diagnosis of refractory TLE due to MTS from the Epilepsy Center surgery series at Hospital São Paulo, Universidade Federal de São Paulo, São Paulo, Brazil. Ninety-one patients submitted to ATL were followed for a mean period of four years (range 2 to 6). All subjects were evaluated before and year-to-year after surgery. The pre-surgical evaluation comprised a semi-structured interview in order to obtain clinical and demographic characteristics, the QOL Brazilian validated "Epilepsy Surgery Inventory" (ESI-55) (Alonso et al., 2006), and the Global Assessment of Functioning Scale (GAF). Engel's classification was used for seizure outcome.

Results: At six months after surgery 47/91 (51.6%) patients were Engel IA, 27/91 (29.7%) Engel IB, and 17/91 (18.7%) remained with seizures; at one year 42/90 (46.7%) were Engel IA, 33/90 (36.7%), IB and 15/90 (16.6%) had seizures; at two years 44/91(48.4%) were Engel IA, 28/91 (30.8%) were Engel IB, and 19/91 (20.9%) continued with seizures; at five years 18/39 (46.2%) were Engel IA, 10/39 (25.6%) IB, and 11/39 (28.2%) still had seizures. The side of resection was not associated with QOL perception. In general, there was a significant improvement ($p<0.05$) in QOL after surgery measured by most of ESI-55 sub-scales. A high correlation between GAF scores and ESI-55 domains was observed. As GAF points were increasing, QOL scores also increased. At six months assessment, analysis of the subgroup of seizure-free patients showed better QOL ($p<0.05$) compared with the other groups (auras and those who continue having seizures), except for Social Function ($p=0.133$) and Emotional Well-being ($p=0.080$) domains. After the first year, all ESI-55 scores were better in the seizure-free group ($p<0.05$), indicating a significant increasing in QOL compared with those patients Engel IB and others. The comparison between the seizure-free group and patients with auras showed that seizure-free patients had better QOL ($p<0.05$) than those who remained with auras in a short-time (first three years of follow-up), while at the four and five year evaluation, QOL was similar in both groups.

Conclusions: Our results support the long-term positive effects of ATL to improve QOL and psychosocial functioning.

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RECENT ADVANCES IN STEREOELECTROENCEPHALOGRAPHY (SEEG)

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Rationale: Despite the remarkable progress of modern neuroimaging some patients with intractable epilepsy require intracranial recording to lateralize or precisely localize the epileptic generator in order to assess candidacy for seizure surgery. In 1977 Talariach and Bancaud reported their technique of stereoelectroencephalography (SEEG). This is a frame-based technique which requires an intra-operative angiogram and is limited to an orthogonal trajectory. Commercial electrodes developed with input from French neurosurgeons are fully MRI compatible. Tailored radiofrequency lesions made through these electrodes prior to removal may obviate the need for craniotomy in some patients.

The electrodes may be removed at the bedside.

Methods: Olivier at the MNI has perfected a novel technique of SEEG placement without a traditional frame or the need for intra-operative x-rays or angiogram. It allows accurate placement in virtually any trajectory and thus fewer electrodes may be necessary. The electrodes we have been using are not MRI compatible. Radiofrequency lesionectomy through these electrodes has not been attempted. An operative procedure is required for their removal.

Results: Experience over the past several years has allowed the adaptation of our method of SEEG placement to commercially available electrodes. This new technique will be demonstrated by intra-operative photographs and post-implantation MRI.

Conclusions: With the fusion of these technologies we may: accurately place fewer electrodes, acquire MRI with the electrodes in place, perform radiofrequency lesions, and avoid a second surgery for removal. This advance permits image-guided stereotaxic resection using MRI acquired with the electrodes in place thus ensuring adequate removal of tissue around specific electrodes and/or specific electrode contacts.

2.243

AMYGDALAR EPILEPSY, COMPARATIVE STUDY

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Rationale: Amygdala plays a central role in the pathogeny and semiology of temporal lobe epilepsy (TLE). Pure amygdalar injuries can induce epilepsy without damage of the rest of medial temporal lobe structures. It is well known that amygdala has prominent connections with structures around, then it is an opened question if in cases with amygdalar epilepsy (AE) a circumscribed steraotactic transsylvian selective amygdalectomy might suffice an might be a valid treatment option in patients with TLE, establishing amygdala as a limbic target in

those selected cases. The aim of this study is to descrive different characteristics and surgery outcome , in our experience, in patients with epilepsy secondary to pure amygdalar epilepsy compared with epilepsy secondary to unilateral mesial temporal sclerosis (MTE).

Methods: We compared clinical, electrical and neuropsychological characteristics (before and after surgery); of 4 patients with AE with regard to 7 patients with MTE treated with surgery and seizure free after 1 year follow up. All surgically treated patients underwent a prolonged video-EEG monitoring with seizure registration.

Results: 11 patients with mean age of 46.5 (SD12.69), age at epilepsy onset 18.82 (SD15.64), seizure frequency (month) 7.55 (SD17.48), referred initial precipitating injury 0/4 (0%) AE compared with 6/7 (85%) MTE (p:0.05), psychic aura in 3/4 (75%) AE vs 2/7 (28%) MTE, nocturnal seizures 2/4 (50%) AE vs 1/7 (14%) MTE, normal intercritic EEG in 3/4 (75%) AE vs 0/7 (0%) MTE (p:0.029), not pre-surgery memory impairment in (75%) AE vs 0/7 (0%) MTE (p:0.029), post-surgery stable memory 2/2 AE vs 3/7 MTE .

Conclusions: Patients with AE refer less initial precipitating injury, usually have psychic aura, their intercritic EEG could be normal and they present less memory impairment with regard to MTE patients. In AE patients selective amygdalectomy is effective and does not produce memory impairment.

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EPILEPTOGENIC ZONES ARE OFTEN FAR REMOVED FROM BRAIN TUMORS: AN INTRACRANIAL EEG ANALYSIS

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Rationale: While seizures are a common finding in patients with brain tumors, the spatial relationships of the tumor and the seizures are not well understood. We analyzed spatial relationship of tumor and seizures in patients who underwent 2-stage epilepsy surgery.

Methods: Patients with brain tumor were included if they underwent 2-stage epilepsy surgery with implantation of intracranial electrodes (ICE). A total of 11 patients were included in the study. The number of ICE placed ranged from 40 to 108, with total of 779 electrodes (all patients combined). Each patient had a pre-op high resolution MRI and a post-implantation CT scan. First, T1W MRI was imported using BrainSuite, the skull stripped away leaving only the underlying brain. After creating a 3-D surface rendering of the brain, it was imported into a custom software package, where a post-implantation CT showing ICE locations was aligned and coregistered to the MRI. The software was then able to overlay the CT onto the MRI of the patient's brain and extrapolate electrode positions. All electrodes were then manually verified using intraoperative photographs to ensure correct placement.

Each ICE was classified as Seizure onset (earliest sustained rhythmic changes on EEG distinct from background), Seizure spread (involved in seizure within 10 sec of onset) or neither. In addition, each ICE was designated as tumor (directly over or within the tumor), peri-tumor (adjacent to tumor) or no tumor. The tumor was also manually outlined on each slice of a pre-operative MRI, and these markings were then turned into three-dimensional renderings by the Smap software. Finally, with the reconstruction of the patient's brain, the electrode locations, and the tumor location, linear distance to tumor was calculated for each electrode in each patient using the Smap software.

Results: When all electrodes were included in the analysis seizure onset electrodes were more likely to be outside of the tumor or peri-tumoral regions. When individual electrodes over the seizure onset region were compared, the tumor vs no tumor location were significantly different, with the seizure onset zone more likely to be over the no tumor region than tumor. Out of 779 total electrodes analyzed across all patients, 73 were on seizure onset (9.4%), 98 on seizure spread (12.6%) and 608 were on neither (78.1 %). The average distance of nearest tumor location for seizure onset electrode was 20.37 mm (SD=14.89), seizure spread electrode was 19.88 mm (SD=19.87) and neither electrodes was 28.50 mm (SD=18.77). The distance information was available on 61 of 77 seizure onset electrodes and it was more than 20 mm from the nearest tumor in 26 (42.62%).

Conclusions: In most centers, patients with brain tumors and epileptic seizures are operated on with a primary goal of removing the tumor. However, since patients with tumors and seizures often have seizure onset regions far from the tumor location (more than 2 cms away in 43%), as a two-stage approach with electrocorticography is needed to also be certain that the patient's epileptic disorder is fully treated.

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SURGICAL TREATMENT OF NONLESIONAL SUPPLEMENTARY SENSORIMOTOR AREA EPILEPSY

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Rationale: Medically intractable non-lesional supplementary sensorimotor area (SSMA) epilepsy remains a challenge of treatment. Its mesial location and proximity to eloquent areas make the complete resection of the epileptogenic zone difficult. We have recently published the results of epilepsy surgery in patients investigated with subdural electrodes, and found that seizures of SSMA origin were a predictor of good outcome, however, this sample included all cases of medically-intractable SSMA epilepsy, including cases with lesions on MRI. This current study examines our surgical experience with non-lesional SSMA epilepsy.

Methods: We retrospectively reviewed all consecutive patients admitted to the epilepsy unit with the diagnosis of non-lesional medically intractable SSMA epilepsy between February 1989 and March 2005. Inclusion criteria included an epileptogenic area exclusively over the SSMA confirmed with intracranial electrode recording and a normal MRI. We excluded all patients with an abnormal MRI. We also describe our surgical technique for mapping and resection of the nonlesional SSMA. Demographics as well as clinical data are presented.

Results: Ten patients (2 females) were included. The mean age at surgery was 24.2 (range: 3 - 41). Mean age of epilepsy onset was 8.1 years of age (range: 1-14). Classic fencing posture was seen in only 2 patients. All patients underwent placement of subdural electrodes prior to surgery. An average of 11 strips (range: 8-13) were placed in each case. Length of hospital stay was 14 days on average (range: 4-26 days). Following the intracranial recordings, all patients underwent awake craniotomy with mapping of the superior and mesial rolandic region and resection of the SSMA. Mean follow up was 23.4 months (SD +/- 15.1). 9 patients had weakness of the contralateral leg and/or

hand immediately after surgery and complete resolution was observed in 7. Two patients did not recover completely. In one patient a very mild hand weakness remained present at follow-up without an explanation on MRI and another patient had an intra-operative infarct as a result of injury to the collosomarginal artery leading to a permanent contralateral foot and shoulder weakness. Transient speech difficulties were seen in only 3 patients following surgery. In the 8 patients in whom follow-up was available, and Engel I classification was obtained in 4 patients (50%), III in 2 patients and IV in 2 patients.

Conclusions: Good surgical results (50% seizure free and 75% improved) were obtained in this small subset of patients with non-lesional SSMA epilepsy. While significant contralateral weakness was almost universal following surgery, nearly all patients recovered completely.

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CORTICAL DYSPLASIA IN PATIENTS WITH TEMPORAL LOBE EPILEPSY; MORPHOLOGICAL STUDY OF 60 CASES

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Rationale: Rationale: In the present study we characterized neocortical malformations in cases of refractory temporal lobe epilepsy and cortical dysplasia (CD)

Methods: We studied 60 cases (40 males and 20 females), mean age 34.6 years, of refractory temporal lobe epilepsy and CD, only 8 with preoperative MR imaging suggestive of CD. All patients were studied according to standardized presurgical protocol and submitted to temporal lobectomy and amigalohippocampectomy. The expression and distribution of GFAP, nestin and vimentin, was studied immunocitochemically in T1, T2, and T3 regions.

Results: We found marked dislamination in all areas of the cortex, neuronal loss, amylaceous bodies, neuronal cytomegaly with cytoskeletal disorganization containing dense fibrillar cytoplasmic aggregates, dysplastic neurons, balloon cells with atypical nuclei, often with binucleation, and abundant glassy eosinophilic cytoplasm. CD was classified as Type IA in 8.3%, Type IIA in 50%, and Type IIB in 15% of cases. Combined Type IA and IIA were found in 5%, Type IIA and IIB in 16.6% and Type IA and IIB in 1.6% of cases. GFAP, nestin and vimentin were highly expressed in the majority of neurons in the cortical areas as well as the hippocampus.The majority of balloon cells were found in the white substance. Expression of nestin was increased only in balloon cells and dysplastic neurons.

Conclusions: These findings suggest that malformations of cortical development, up regulation of the astrocytic response as an astroglial dysfunction, and possible alterations in the blood brain barrier contribuite to high epileptogenic activity in these patients.

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STIMULATION OF THE ANTERIOR NUCLEUS (AN) OF THE THALAMUS FOR EPILEPSY DOES NOT APPEAR TO PROMOTE ADVERSE VENTILATORY CHANGES DURING SLEEP

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Rationale: Results of chronic cyclic AN thalamic stimulation thalamus was recently reported in Epilepsia (the SANTE study); overall results were positive. The thalamus is a critical structure in sleep, exploring changes in sleep-related physiological parameters (including breathing) is important in evaluating device safety. Sleep apnea can exacerbate epilepsy. Patients with apnea will likely be candidates for AN-stim. Our study evaluates potential sleep-related ventilatory changes in the SANTE cohort. Our goals were: (1) to determine if those receiving AN-stim had more hypopneas or apneas than matched controls, and (2) to determine if hypopneas or apneas appeared central or obstructive in origin.

Methods: 4 patients receiving AN-stim and 4 matched controls with epilepsy were studied with standard PSG (and a full EEG montage) for 2 nights. Although the total number of days of recording was 16, only 8 nights of recording generated reliable data for measurement of ventilatory changes and determination of cause (central v. obstructive). All underwent ambulatory PSG+EEG. All wore a nasal thermistor, an SaO2 pulse-ox, and effort sensor belts at the chest and abdomen. PSG scoring was performed using Nihon-Kohden, Polysmith ™ software.

Results: Among the AN-stim patients, the longest events for each of the 4 nights, were a 78 s (second) obstructive hypopnea (OH) with a minimum SaO2 of 97%, a 78 s OH with a minimum SaO2 of 96%, a 47 s mixed apnea with a minimum SaO2 of 96%, and a 78 s OH with a minimum SaO2 of 96%.

The lowest SaO2 values were a 90% associated with a 78 s OH, an SaO2 of 81% associated with a 10 s OH, an SaO2 of 95% associated with a 12 s central apnea, and an SaO2 of 87% associated with a 77 s mixed hypopnea.

For comparison, among the non-stimulated, the longest events for each of the 4 nights of recording were as follows: a 17 s OH with a minimum SaO2 of 90%, a 76 s OH with a minimum SaO2 of 95%, a 77 s OH with a minimum SaO2 of 93%, and a 78 s OH with a minimum SaO2 of 93%.

The lowest SaO2 values were a 90% associated with a 17 s OH, an SaO2 of 93% associated with a 71 s OH, an SaO2 of 85% associated with a 57 s obstructive apnea, and an SaO2 of 89% associated with a 35 s OH.

Conclusions: Patients receiving AN-stim do not appear to have an increased incidence of sleep-related ventilatory disruption. During the long events, the lowest SaO2s were found in controls. AN-stim patients had a slighter higher incidence of central apnea (1) although the longest central apnea was only 12 sec. (SaO2 fell only to 95%). The small (n) precludes statistical analysis. The events were longer than expected; the event times are likely overestimates due to the detection software which is extremely sensitive to minor ventilatory changes. Nevertheless, the Medtronic SANTE device does not appear to provoke adverse ventilatory changes in sleep. Ongoing studies are in

progress that may uncover other changes in sleep behavior related to the device.

Events by length-type-SaO2, and by SaO2-type-length for SANTE patients and matched controls

IMAGE: tables/899599_T1.jpg

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A NEW PERCUTANEOUS SURGICALLY IMPLANTED SYSTEM FOR TRIGEMINAL (V3) NERVE STIMULATION IN HUMAN EPILEPSY

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Rationale: While vagal nerve stimulation has been widely used to treat epilepsy, other cranial nerve stimulation methods, specifically trigeminal nerve stimulation, have been successful in rodent models of epilepsy. Trigeminal manipulations and pilot studies with transcutaneous electrical stimulation have explored the possibility that trigeminal nerve stimulation in humans may benefit refractory epilepsy. One of the authors (MC) has experience accessing the trigeminal nerve in a novel manner to place a stimulation system for the mandibular branch of the trigeminal (V3) nerve for patients with trigeminal neuralgia. Here we present what we believe to be the first such report of a surgically implanted device for trigeminal nerve stimulation in human epilepsy.

Methods: The patient is a 40-year-old woman with medically refractory epilepsy. Her seizures have involved clustered nocturnal events early in sleep of dystonic posturing of the right arm and leg with occasional generalization, often preceded by a sensory change in the face. They had been nightly with perimenstrual worsening despite three AEDs. MRI revealed a focal cortical dysplasia in the left precentral gyrus. Prior surgical work-up included subdural grid LTM. Seizure onsets involved the left primary sensory cortex. She underwent multiple subpial transections of the sensory cortex with transient abolition of seizures. Due to continued refractory seizures, she underwent percutaneous placement of bilateral Medtronic (model 37712) subcompact electrodes that pass immediately adjacent to the mandibular branch of V3. The patient had her usual seizures until the initiation of stimulation, 8 days post-op, with continuous mode bilateral stimulation at 100 Hz with amplitude adjusted to sub-threshold of sensation. The patient's seizure frequency, seizure types, and side effect burden have been monitored in this unblinded pilot.

Results: Lead placement was well tolerated. Postoperative local pain was manageable and improved over time. Tongue tingling and enhanced salivation were reported as mild side effects. Seizures lessened in frequency and in severity within days of activation. Seizures became every 2-3 days (instead of daily), and changed to complex partial events of staring only, though continued to arise from sleep. Seizures still clustered at 0-3 per night when present.

Conclusions: Direct bilateral stimulation of the trigeminal nerve is feasible and well-tolerated in a patient with refractory epilepsy, just as in those with trigeminal neuralgia. Side effects were mild and tolerable. Seizures were notably diminished both in number and in severity. This percutaneous technique presents advantages to vagal nerve stimulation and transcutaneous trigeminal stimulation. Leads are easily placed and removed, in comparison with vagal nerve stimulation. They are cosmetically inconspicuous and likely will permit lower current settings and greater durability than transcutaneous methods. This report will likely stimulate a broader evaluation of the acceptability and applicability of this method in refractory epilepsy.

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RESECTIVE EPILEPSY SURGERY IN PATIENTS WITH PERIROLANDIC EPILEPSY

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Rationale: To assess the efficacy and safety of resective epilepsy surgery in unselected patients with both lesional and nonlesional perirolandic epilepsy.

Methods: We identified 15 consecutive patients who underwent perirolandic cortical resection (without multiple subpial transections) for intractable epilepsy between 1995 and 2009. This number represents 5.2% of all resective epilepsy surgeries at Brno Epilepsy Center. Detailed analysis was performed in 13 patients with minimal postoperative follow-up 2 years (average 7 years, std. 4.1). The average age at the time of surgery was 27 years (range 13-50 years). Preoperative MRI disclosed restricted lesion in the perirolandic cortex in nine patients, in four subjects repeated thorough neuroimaging investigation failed to identify any structural pathology. Most patients underwent preoperative chronic invasive video-EEG (70%). Advanced neuroimaging (incl. fMRI, SISCOM, MRSI, VBM, etc.) was gradually introduced into preoperative set-up and completed whenever possible.

Results: At last follow-up 9 patients were seizure-free - Engel class I (70%), 2 patients were in class II (15%), and 2 patients in class IV (15%). Postoperative neurological deficits were present in 4 patients (30%). In all these cases intensive rehabilitation resulted in a significant improvement, still mild functional deficit remains in 2 patients (15%).

Conclusions: Resective epilepsy surgery is an effective and relatively safe therapeutical strategy in properly selected patients with intractable perirolandic epilepsy. This can be concluded for both lesional and nonlesional cases. Intensive multimodal preoperative investigation (incl. invasive EEG, cortical mapping, fMRI, SISCOM, VBM, etc.) and peroperative stereotactic navigation promise to further decrease a significant risk for residual functional deficit.

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REVIEW OF PREDICTIVE FACTORS FOR SUCCESSFUL EPILEPSY SURGERY BASED ON MRI, ROUTINE ELECTROENCEPHALOGRAM AND CLINICAL FACTORS

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Rationale: Resective surgery is an important consideration for patients with treatment resistant epilepsy as it may offer the best chance for seizure freedom. Initial patient counseling and the decision to refer a patient to an epilepsy surgery center is usually based on the history and physical exam, routine electroencephalogram (EEG), and brain MRI. The aim of this review is to summarize the literature and identify

factors typically available in the general office setting that are reliable predictors of epilepsy surgery outcome.

Methods: A literature search was performed using Pubmed and Embase. Inclusion criteria included: English language, sample size e”20 patients, MRI performed on e”90% of patients, a median age e”16 years, average of e”1 year follow-up, and predictive value assessment of clinical factors, routine EEG and/or MRI brain for outcome in epilepsy surgical resections. Articles were independently reviewed by at least 2 authors and data on study design and predictive factors were abstracted.

Results: Of the 2,248 articles related to predictors of epilepsy surgical outcome identified, 123 met all inclusion criteria. Only 12 articles had a prospective study design. Study populations varied in size and epilepsy characteristics with the majority focusing on mesial temporal lobe epilepsy or lesional epilepsies. The studies focused almost exclusively on patients that had undergone resection rather than all patients considered for surgery or undergoing invasive procedures (intention-to-treat analysis). Predictive factors were not uniformly assessed in most studies, nor were they uniformly defined across studies. For example, in various studies, unilateral routine EEG epileptiform activity was variably categorized as “only ipsilateral spikes”, “>70% ipsilateral”, “>80% ipsilateral”, or “>90% ipsilateral”. Although many studies used the Engel or modified Engel classification systems, many utilized non-standardized outcome determinations (e.g. “good”). Only 6 studies had a masked assessment of seizure outcome following surgery.

Conclusions: The heterogeneous patient populations, methodologies and outcome determinations significantly limit the existing literature’s ability to predict the likelihood of a patient achieving seizure freedom from resective surgery based upon pre-operative data, especially in patients with extra-temporal non-mesial epilepsy. Prospective multicenter studies based upon intention to treat (i.e. enrolling patients prior to invasive procedures to determine the number of patients that are considered for epilepsy surgery that do not progress to a resective procedure) are necessary to better facilitate and encourage early referral to comprehensive epilepsy centers, counsel patients and families and identify new strategies for improving outcomes. By establishing and utilizing accepted, standardized definitions (e.g. treatment resistant epilepsy), one can improve the generalizability of findings across patients and centers.

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DRUG WITHDRAWAL PROTOCOL AFTER TEMPORAL LOBE EPILEPSY SURGERY

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Rationale: It is established that temporal lobe epilepsy surgery is effective to reduce or eliminate seizures in almost two thirds of drug resistant patients 1,2. Despite of the debates around this subject, little information is available regarding the best way to perform antiepileptic drug (AED) withdrawal in those patients who become seizure free after surgery 2,3. A protocol of drug withdrawal was applied in patients after two years of follow up and data are presented and discussed.

Methods: Patients with clinically intractable temporal lobe epilepsy (TLE) submitted to surgical treatment who became seizure free for a period of two years 4 and had serial EEG exams without epileptic discharges were candidates to be submitted to the protocol of AED withdrawal. Patients and their families were informed about the risks and got into the protocol after informed consent.At first step we took off benzodiazepines, followed by AED which were not considered first choice for clinical treatment of TLE, and finally AED that were first choice for TLE, such as carbamazepine, oxcarbazepine and phenytoin. The withdrawal was performed gradually and the drug was reduced 25% of the total dose in a period of five half-lives of the drug. After each step the EEG was repeated. In patients whose EEG showed epileptic discharges the withdrawal was stopped and in those whose seizures recovered the AED were re-introduced integrally. Patients were followed and analyzed prospectively for a mean period of two years (range 0.5 to 4 years).

Forty patients were included, 32 were submitted to anterior temporal lobectomy (ATL), four to ATL plus lesionectomy, one to selective amygdalohippocampectomy and three to lesionectomy alone (Table 1).

Results: In the last follow up, 20 (50.0%) were seizure free without AED; 5 (12.5%) were tapering medication; 4 (10.0%) the withdrawal was interrupted because epileptic discharges appeared in EEG and in 11 (27.5%) seizures occurred (Table1). In the latter group, 10 (25.0%) reached seizure control after reintroduction of AED and in 1 seizures were frequent despite the use of AED.

Conclusions: Our results are compatible with data available in literature 1,2,3,4 representing a safety protocol since from the 40 patients included, 72.5% did not have seizure recurrence, and 50.0% are seizure free without medication. Finally, after seizure recurrence only 9.0% showed refractoriness.

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DRUG-RESISTANT EPILEPSY, NEUROCYSTICERCOSIS AND MESIAL TEMPORAL SCLEROSIS: VARIATIONS ON THE THEME OF DUAL PATHOLOGY

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Rationale: Neurocysticercosis (NCC) infection is a leading cause of seizures in developing nations and is now recognized as an emerging cause of seizures in the U.S. Indeed, one recent study suggests that NCC accounts for up to 10% of patients presenting to emergency departments with seizures in the southwestern U.S.(Ong *et al* 2002). There are several potential mechanisms relating NCC and drug-resistant epilepsy (DRE), however, and a number of authors have reported an association between NCC and mesial temporal sclerosis (MTS) (Singla *et al* 2007). We report a series of patients with DRE referred for presurgical evaluation who demonstrate evidence of both remote NCC and MTS.

Methods: Patients with DRE cared for in our tertiary care epilepsy clinic at LAC+USC in addition to surrounding Los Angeles Department of Health Services facilities are routinely referred for presurgical evaluation at Rancho Los Amigos National Rehabilitation Center. All patients undergo inpatient video-EEG monitoring (VEM), high-resolution MRI, CT or PET-CT, and neuropsychological evaluation as part of a standard presurgical evaluation.

Results: Approximately 5%(13/200) of patients referred for medically intractable epilepsy over two years demonstrated evidence of remote NCC and MTS. All patients with dual pathology had emigrated from countries with endemic NCC. In 12/13 cases of dual pathology,

punctuate calcifications consistent with remote NCC were present in the hemisphere ipsilateral to MTS, frequently below the Sylvian fissure or at the temporal-occipital junction. In two cases, punctuate calcifications were associated with extensive areas of abnormal T2/FLAIR signal abnormality in addition to MTS. In almost all cases, ictal onset as determined by video-EEG monitoring was localized over the anterior temporal region coincident with MTS. One patient demonstrated a punctate calcification deep within the left temporal lobe associated with a superficial area of encephalomalacia with contralateral ictal onset. Ictal onset did not localize to extratemporal calcifications in any patient with dual pathology. Six patients have undergone standard anterior temporal lobe resection with limited amygdala-hippocampectomy. One patient experienced a single post-operative complex partial seizure, but subsequently achieved seizure-freedom (1 year at present). All remaining patients remain seizure-free since surgery and all are maintained on anti-convulsant medications.

Conclusions: 1.NCC is rarely a cause of DRE and any patient who presents with DRE should be considered for standard presurgical evaluation including MRI and VEM. 2.Although the precise causal relationship between NCC and DRE is unclear at the present time, close proximity of punctate calcifications and MTS suggests that the latter may represent a sequelae of repetitive focal seizures, interictal discharges and/or focal inflammation. 3.The presence of dual pathology (MTS and NCC) does not preclude resective surgery, and many patients enjoy post-operative seizure freedom following standard temporal lobectomy.

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REOPERATION FOR FAILED EPILEPSY SURGERY: OUTCOME IN PATIENTS WITH REFRACTORY TEMPORAL LOBE EPILEPSY

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Rationale: Epilepsy surgery is currently the most effective overall treatment for patients with refractory partial epilepsy. Although more than 60% of patients become seizure free after receiving anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy (SAH), the remaining patients experience recurrent seizures after surgical treatment. For those who failed the first surgery, further treatment options are quite limited, and at times, second surgery may improve seizure outcome. We reviewed our surgery patients to document the success of reoperation after failed ATL and SAH and to identify favorable prognostic variables influencing good seizure outcome.

Methods: Data were obtained retrospectively from our epilepsy surgery database at the Barrow Neurological Institute between 2004 and 2009. In order to present more uniform patient population, we included patients who had temporal lobe surgery initially followed by second surgery for seizure control. Patients with minimum of 12 months follow up were included in the study. Demographic details, seizure history, presurgical evaluation, and postoperative follow up data were evaluated.

Results: 6 patients with temporal lobe epilepsy were identified from our database that had second resective surgery and met the other criteria. The initial surgery was ATL in 3 of 6 patients and SAH in the remaining 3. Before the initial surgery, all 6 patient's brain MRI scans showed suggestive findings of mesial temporal sclerosis. Recurrence of seizure occurred within the first postoperative year in 5 out of 6 patients. Repeat MRI brain prior to second surgery showed residual amygdala and hippocampus in all 6 patients. Phase II evaluation with depth electrodes confirmed the ictal onset from the remnant tissue. All patients underwent complete resection of the remnant temporal lobe including mesial temporal structures and ipsilateral anterior temporal lobe. Seizure outcome after second surgery is more favorable if the initial surgery was SAH (N=3), of which 2 patients (N=2; 66%) has Engel Class I (free of disabling seizures) and 1 patient (N=1; 33%) has Engel Class 2 (rare disabling seizures) seizure outcome. Significant improvement was seen even in patient who had ATL (N=3) of which 1 patients (N=1; 33%) has Engel Class 2 and 2 patients (N=2; 66%) has Engel Class 3(worthwhile improvement) seizure outcome.

Conclusions: Second resective surgery for epilepsy has favorable seizure free outcome in patients with temporal lobe who failed initial surgery, especially those who failed SAH. Phase II investigations prior to reoperation can provide useful information in identifying

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UTILIZING A DECISION TREE MODEL TO PREDICT OUTCOME FOR PATIENTS ASSESSED FOR EPILEPSY SURGERY WITH EEG, MRI AND IQ AS FACTORS

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Rationale: Resective surgical treatment can be curative in a large subset of patients with treatment resistant epilepsy. There is a need for a simple surgical grading tool which can be employed by the referring neurologist, ideally utilizing information obtained prior to diagnostic hospitalization. Our hypothesis was that a model using interictal EEG, brain MRI, seizure semiology and IQ could stratify patients with treatment resistant epilepsy with respect to their likelihood of achieving seizure freedom following assessment for resective epilepsy surgery.

Methods: A prospectively identified cohort of 211 patients from the University of Alabama was combined with a retrospectively identified cohort of 193 consecutive patients at New York University presented in surgical multidisciplinary conference and either proceeded to surgery or were excluded as surgical candidates. All met inclusion criteria: age e"18, focal epilepsy diagnosis e"2 years, failed e"1 medication, e"1 seizure 3 months prior to admission, follow-up>6 months. Patients were classified as seizure free following resective surgery or not seizure free following resective surgery/no surgery. Pre-operative EEG, MRI, seizure semiology and IQ data were reviewed, systematically categorized (Table 1) and were utilized in a decision tree algorithm to predict seizure freedom. When $p<0.05$ was utilized, a simplistic dichotomous algorithm resulted. Therefore, to further explore, a relaxed, exploratory statistical significance level of $p<0.25$ was used. Nodes resulting in >50% of patients becoming seizure free were considered predictive of seizure freedom.

Results: The overall seizure freedom rate was 46.8%. The exploratory decision tree analysis (Figure 1) resulted in two EEG groups: F, G, H

(bilateral temporal, bilateral extra-temporal, bisynchronous; node 2; N=97) versus all others (node 3; N=307). For node 3, MRI was employed for further stratification: b (unilateral mesial temporal sclerosis (MTS); node 4; N=75) versus all others (node 7; N=232). Node 4 was further stratified based upon IQ: below 70 (node 5; N=11), above 70 (node 6; N=64). Semiology had no statistically significant impact.

The model correctly predicts outcome in 62% of patients, yielding a positive predictive value of 55%, and a negative predictive value of 71%, with sensitivity of 74% and specificity of 51%.

Conclusions: The relatively low overall seizure freedom rate is due to the fact that patients considered for, but ultimately not undergoing, surgery were included in the analysis, which better reflects the actual decision process for patients and neurologists. Of interest, the model fails to identify the commonly considered "best surgical" group of unilateral MTS with concordant interictal activity as a unique node. Notably, the main predictive factor was interictal EEG; other factors were only statistically viable with a more exploratory statistical approach. The positive and negative predictive values in this model are probably not sufficient for clinical use.

Categorization of Variables

IMAGE: tables/906156_T1.jpg

IMAGE: images/906156_A.jpg

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FRONTAL LOBE EPILEPSY SURGERY: FACTORS INFLUENCING OUTCOME

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Rationale: Surgical management of epilepsy of frontal origin carries unique difficulties, associated with the ill-defined frontal seizure semiology, the intrinsic frontal lobe epileptogenic synchronicity, and the large frontal lobe volume. Surgical outcome of frontal lobe epilepsy is worse than the one of temporal epilepsy. Identification of any factors affecting outcome of frontal epilepsy surgery is of paramount importance for improving outcome.

Methods: Between 1981 and 2006, 79 patients undergoing 81 resections as treatment for medically refractory frontal epilepsy were included in our retrospective study. Variables studied in 31cases with normal imaging studies were (1) spatial concordance of non-invasive and invasive electrographic data, (2) invasive electrographic data alone, (3) age range at surgery, (4) seizure frequency, and (5) seizure duration. Variables studied in 50 cases with structurally abnormal imaging studies were (1) spatial concordance of non-invasive and invasive electrographic data, (2) invasive electrographic data alone, (3) age range at surgery, (4) seizure frequency, and (5) seizure duration. Extent of resection was also studied.

Results: Of 12 non-lesional cases with concordance (C) or partial concordance (PC) of electrographic data, 8 (67%) were Class I outcomes. Of those 15 cases with non-concordance (NC) or discordance (DC) of electrographic data, 1 (6.7%) was a Class I outcome. Of 10 cases with subdural +/- depth electrode localization, 5 (50%) were Class I. Of 17 with depth electrode localization, 4 (23.5%) were Class I. Of 9 cases d" 18 y.o., 3 (33%) were Class I. Of 21 cases > 18 y.o., 6(28.5%) were Class I. Median seizure duration was 12 yrs in seizure free cases and 18 yrs in non-seizure free cases (Table 1). Median seizure frequency was 30/mo in both seizure free and non-seizure free cases (Table 2). There were 34 cases with non-tumor structural lesions and 16 tumor cases. SD +/- depth monitoring was done in 11 cases and depth monitoring alone was done in 2. There was insufficient concordance data for analysis. There was also insufficient invasive monitoring data for analysis (ictal localization in only 8 of 13 cases). Of the non-tumor lesional cases, 5 (71.4%) of 7 d" 18 y.o. were Class I and 10 (41.7%) of 24 > 18 y.o. were Class I. Of 12 tumor cases 9 (75%) were Class I (only 3 were d" 18 yo). Of 22 complete resections in non-tumoral cases 13 (59%) were Class I (2 incomplete resections with follow-up data). Three (60%) of 5 complete tumor resections were Class I and 6 (85.7%) of 7 incomplete resections were Class I.

Conclusions: Concordance of non-invasive and invasive electrographic data was the most important determinant of outcome in non-lesional cases. Completeness of lesion resection in this series did not yield significantly better outcome. Younger patients were more likely to have Class I outcomes in non-tumor lesional cases. Tumor cases were more likely to have Class I outcomes compared to non-tumor lesional cases. Shorter seizure duration favored Class I outcomes in the non-lesional and non-tumor lesional cases.

Table 1

IMAGE: tables/907435_T1.jpg

Table 2

IMAGE: tables/907435_T2.jpg

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EPILEPSY SURGERY IN ADULTS WITH MEDICALLY INTRACTABLE TEMPORAL LOBE EPILEPSY IN CROATIA

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Rationale: Epilepsy surgery is an effective option for the patients with medication refractory temporal lobe epilepsy. Earlier studies showed that careful selection of potential candidates can improve their long-term outcomes.

Methods: We analyzed patients undergoing presurgical evaluation and epilepsy surgery at the University Hospital in Croatia. Preoperative evaluation included detailed clinical history, long-term video-electroencephalography, brain 1.5 or 3T MRI with epilepsy protocol, interictal PET/CT scan and neuropsychological testing. Collected demographic and clinical data included patients' age, age of epilepsy onset, duration of epilepsy, age at surgery, seizure frequency rate, presurgical evaluation data, pathohistology of resected specimen and post-surgical outcomes. All patients had failed at least 2-3 antiepileptic drugs and had a minimum of monthly seizure rates. Seizure outcome was based on the modified Engel scale.

Results: Epilepsy surgery program at our University Hospital started in November 2009. Since then we performed, on average, 2-3 epilepsy surgeries each month. Mean age of patients at the time of surgery was 32 years, 60% were females and mean duration of epilepsy was 22 years. All subjects had full concordance between interictal and ictal

video-EEG data, MRI, PET and memory evaluation. Hippocampal sclerosis was identified with MRI investigations and confirmed in pathological resections in 86% of patients, oligodendroglioma in 1 patient, and a cystic malformation in the temporal lobe in 1 patient. Eighty-six percent of patients had a selective amigdalohippocampectomy, 61.5% on the left side. Ninety-three percent of patients had a satisfactory seizure outcome (Engel 1 and 2). Transient neurological complications occurred in 1 patient (sensory dysphasia) and surgical complications occurred in 1 patient (haemorrhage), but without permanent sequelae.

Conclusions: We present the first epilepsy surgery for refractory temporal lobe epilepsy results from Croatia. Seizure-free rates and outcomes are similar to those reported in other studies.

2.257

SURGICAL OUTCOMES FOR POST-TRAUMATIC EXTRA-TEMPORAL EPILEPSY SURGERY

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Rationale: Brain trauma is a significant risk factor for epilepsy. Post traumatic epilepsy can be refractory to anti-epileptic drugs, making surgical treatment a potential treatment option. While post traumatic pathology is often extra-temporal, little has been reported in success rates of surgical evaluation and treatment of extra-temporal post traumatic epilepsy. Here we report a large series of such cases.

Methods: We performed a retrospective review of patients who had video EEG monitoring done at University of Washington Regional Epilepsy Center at Harborview and University of Washington between 1990 and 2007. We identified subjects who: 1) had a clear history of antecedetal head trauma, 2) no other plausible etiology for their epilepsy, and 3) age 18 at the time of monitoring.

Results: Overall, 371 patients met these criteria. A total of 99 patients were offered surgery. Seventy seven (77) had temporal lobe resection, the remainder had some resection of extra temporal regions (with or without inclusion of some temporal lobe). Of the 32 patients 7 were found to have pathological evidence of another process (such as dysplasia) after resection. Of the remaining 25 patients, 20 had invasive monitoring. Among these, 24% were seizure free on long term follow up. Altogether, about

half of the patients have had a favorable outcome with no or less than 2 seizures per year. Surgical procedures were considered challenging due to presence of adhesions and prior surgery and brain injury. Complications included post-implantation subdural hematoma requiring evacuation (1 case), post-operative infection requiring absecss drainage (1 case), and occurence of both (1 case). Factors associated with good outcome included frontal lobe resection, concordance of EEG and MRI, and late age of onset for trauma.

Conclusions: A significant portion of post-traumatic intractable epilepsy appears to be extra-temporal. Surgical treatment of extra-temporal post traumatic epilepsy is feasible and relatively safe and overall has similar outcome to extra-temporal lobe resections. Seizure freedom rate is lower than many other groups with more focal pathology. Distinction of these groups and resection often require invasive monitoring, which in this population is challenging and carries a risk of complictions in a minority of patients.

2.258

CLINICAL FEATURES AND PATHOLOGICAL CHARACTERISTICS OF AMYGDALA ENLARGEMENT IN MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Although the hippocampus is considered as an important site of seizures in mesial temporal lobe epilepsy (mTLE), the amygdala may also play a significant role in the epileptogenesis of mTLE. Amygdala enlargement is often found in patients with mTLE, and volumetric detection of amygdala enlargement has been documented in 'image-negative' TLE patients. However, only limited data have been reported on the clinical features, surgical outcomes, and pathological characteristics in mTLE patients with amygdala enlargement.

Methods: We recruited epilepsy patients who had undergone surgical treatment for refractory epilepsy with radiological evidence of amygdala enlargement. All patients showed homogenously increased amygdala volumes on MRI without enhancement and underwent surgical treatment for mTLE.

Results: A total of 12 patients were included, and 11 became seizure free. Pathology results revealed that eight patients had focal cortical dysplasia (FCD), two had ganglioglioma, one had oligodendroglioma, and one had astrocytoma. The clinical features, MRI findings and clinical features were largely indistinguishable between the patients with brain tumors and those with FCD, but the patients with brain tumors tended to be younger at the time of seizure onset.

Conclusions: Our study showed that surgical treatment of epilepsy in patients with amygdala enlargement usually has a favorable outcome. FCD was the most frequent pathological diagnosis in these patients. However, a brain tumor should be considered in the differential diagnosis, especially in young patients, because it is often difficult to differentiate FCD from a brain tumor in radiological findings.

2.259

NO INFECTION IN 100 CONSECUTIVE CASES OF VAGUS NERVE STIMULATION FOR TREATMENT OF REFRACTORY EPILEPSY

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Rationale: Since vagal nerve stimulation was added into the surgical armamentarium for treatment of refractory epilepsy, infections have been reported in 1-6% of cases. However, our group has completed 100 consecutive cases without infection.

Methods: All our patients are subjected to standardized presurgical evaluation; 7 or more Electroencephalogram, Video-Electroencephalogram, polisomnography, neuropsycological tests (patients able to cooperate) and MRI, as well as SPECT and PET in selected cases. VNS implantation in the left cervical vagus nerve is done under general anesthesia, with a one-day in hospital admittance. We routinely use antibiotic, cloramphenicol 1g/L(when contraindicated spreptomycin) in all irrigation solutions as well as prophylactic antibiotic (cephalothin in the younger age group and a fourth generation

quinolone in adults), three doses on the surgical day continued for 10 days orally. Mean interval between implantation and start of stimulation, at minimal parameters, is fifteen days. Follow-up is carried out 4-6 weeks to adjust stimulation parameters, record seizure characteristics/frequency, on-demand use of magnet, and assess QoL.

Results: All 100 systems were successfully implanted, 30 in the young age group (age range 2-20) and 70 in adults (range 21-54). Adverse effects included transitory cough and voice changes. Wounds healed unremarkably and no infections were registered. The use of antibiotic as well as a good surgical procedure with little incisions and minimal trauma to the tissues is the hallmark. Additionally we have had two battery replacements and one complete system exchange without infection. This series of patients responded to treatment very similarly to our previously reported series with a responder's rate of 72%, 58% among the generalized seizure group, and 84% in the partial seizure group. We have two patients who are seizure free, and 14 with over 90% improvement. The follow up on these cases was 14-108 months (mean 40)

Conclusions: We believe that given good selection of candidates, a careful surgical procedure, use of prophylactic antibiotic and assurance of compliance to antibiotic postsurgical scheme, infection rate for VNS should be nil.

2.260

OUTCOME OF TEMPORAL LOBECTOMY FOR HIPPOCAMPAL SCLEROSIS IN OLDER PATIENTS

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Rationale: Older adult patients account for a very small percentage of patients who have received surgical treatment for epilepsy. Previous reports of seizure outcome in elderly included heterogeneous pathologies. There have been few studies reported outcome of surgery for hippocampal sclerosis (HS) in older patients.

Methods: We retrospectively reviewed patients who underwent surgical treatment for medially refractory temporal lobe epilepsy at King Chulalongkorn Memorial Hospital between January 2004 and March 2009. Study inclusion criteria consisted of patients who were 16 years or older, had unilateral HS and no other lesions on magnetic resonance imaging (MRI) and pathologically proven hippocampal sclerosis. All patients had a minimum of 1-year follow-up.

All patients underwent a complete neurologic history and physical examination, MRI and 24-hour scalp video electroencephalography (EEG) monitoring. Wada test, single photon emission tomography (SPECT) and positron emission tomography (PET) were performed in selected patients. The procedures performed were anterior temporal lobectomy (ATL). Invasive monitoring with implanted subdural electrodes was performed whenever noninvasive recordings were nonconcordant. All surgeries were performed by a single neurosurgeon and surgical pathology was obtained in all patients.Seizure outcome was classified according to Engel's classification based on their last postoperative seizure status. Patients were divided into 2 groups: seizure-free (Engel 1) and not seizure-free (Engel 2-4).

Results: A total of 200 patients fulfilled the inclusion criteria. Sixteen patients were older than 50 years (mean age, 55.5 years) and 184 patients were younger than 50 years (mean age 32.9 years). There was no significant difference between the two groups in gender, side of surgery, length of follow-up and history of febrile seizures.

The mean onset of seizure was 13.1 years in younger than 50 age group and 24.7 years in the older group (p=0.019). The mean duration of epilepsy prior to surgery was 20.0 years in the younger than 50 age group and 30.8 years in the older age group (p=0.010). There were no predictors associated with outcome but duration of epilepsy had a trend to be statistically significant (p=0.061).

Nine of the 16 older patients (56.3%) had seizure free outcome compare with 79.4% of the younger patients (p=0.041)(Table 1). Surgical complications in the older age group were significantly higher than young age group (p<0.001).All complications were transient and there was no mortality.

Conclusions: Surgical treatment of TLE-HS in elderly patients offers a chance of seizure-free but lesser than younger patients. Surgical treatment of TLE-HS should be considered as early as possible to maximize the outcome.

Univariate analysis of seizure outcome

IMAGE: tables/884007_T1.jpg

2.261

MANAGEMENT OF EXTRA-AXIAL FLUID COLLECTIONS AFTER SUB-DURAL ELECTRODE PLACEMENT

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Rationale: The placement of intracranial electrodes is an integral part of the pre-surgical evaluation of patients with imprecisely defined relationships between lesion and ictal onsets or those where no lesion is visible on imaging. Subdural grid electrodes (SDEs) are used for this purpose at most epilepsy centers in North America. SDE implantation is associated with a not-insubstantial risk of the collection of sympotomatic extra-axial fluid/blood collections (EFC) in adult populations. In most such situations, the electrodes are removed, interrupting the evaluation that was initially planned. We sought to determine if SDEs could safely be left in place after the evacuation of EFC, and subsequently used to plan a resective surgery.

Methods: Data were collected for all consecutive adult patients undergoing SDE implantation over a 5.5 year period by the senior author. Demographics, numbers of electrodes implanted, records of prior cranial surgery, hemisphere of implantation, duration of monitoring, and occurrence of bleeding complications or infections were tabulated. Relationships of numbers of electrodes, age, and prior surgery with bleeding risk were all assessed. All patients routinely underwent MR scans at 1.5T and Ct scans post-implantation to assess locations of the SDEs and the presence of EFCs.

Results: 65 craniotomies were performed in 60 patients (5 were bilateral) for SDE placement. A mean of 103 electrode contacts (SD 19) were placed, for a mean duration of 9 days (SD 5). Imaging revealed EFCs in almost 70% of cases. In only 4 cases, were the EFCs neurologically symptomatic. In all cases the craniotomy was re-opened, the hematoma and fluid were evacuated, hemostasis was re-accomplished and electrodes were left in situ for subsequent recordings. All 4 of the patients re-operated for EFC underwent definitive resective surgery based on data collected with the same recording electrodes

during the same hospital stay. Of the 60, in 2 cases there were concerns for infection that led to premature electrode removal. Neither of these were patients that had symptomatic EFCs

Conclusions: The process of implanting electrodes is time and material intensive. We show here that even in cases where EFCs are large enough to produce neurological compromise, they may be removed with the possibility of carrying forth the original plan of obtaining intracranial recordings.

2.262

SEIZURE OUTCOME AFTER TEMPORAL LOBE EPILEPSY SURGERY. COMPARISON BETWEEN THE ENGEL AND THE PROPOSED INTERNATIONAL LEAGUE AGAINST EPILEPSY CLASSIFICATIONS

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Rationale: Temporal Lobe Epilepsy (TLE) is the type of partial epilepsy with the most favorable surgical outcome in adults. Surgical outcome is universally reported by using the Engel classification. Nevertheless, outcome reports from multiple epilepsy centers do not distinguish the subclasses (i.e. IA, IB, etc), not allowing for easy identification of patients completely seizure free after surgery. The proposed classification by the International League against Epilepsy (ILAE) aims at identifying such patients readily, and easily differentiating them from patients with post operative auras or with seizure recurrences compared with baseline seizure counts.

Methods: Using a retrospective review, we compared these two classifications using a series of patients who underwent temporal lobe resections for temporal lobe epilepsy.

Patient outcomes were classified using the Engel classification (including subclasses) and the proposed ILAE classification on a yearly basis on the anniversary of the surgery. Only patients in whom one year or more of data was available were included.

Results: 29 patients were included (51% males) who underwent standard temporal lobectomies (51% left). The median age of epilepsy onset was 13 years old, median age at time of surgery was 37 years old and the median latency between epilepsy onset and epilepsy surgery was 18 years. Seizure outcomes were included for years 1 and 2 after surgery (Table 1)

Conclusions: The Engel Classification of seizure outcome overestimates the number of patients who are truly seizure free after temporal lobectomy when the subcategories are not used consistently. The ILAE classification of seizure outcome allows for fast and easy identification of patients completely seizure free after epilepsy surgery. Longer follow up of these patients is needed to determine if this classification could predict true long-term (>5 years) seizure freedom

Outcome comparison

IMAGE: tables/905996_T1.jpg

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REFRACTORY EPILEPSY DUE TO MENINGIOANGIOMATOSIS AND FOCAL CORTICAL DYSPLASIA TREATED BY A STAGED SURGICAL APPROACH

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Rationale: Meningioangiomatosis (MA) is a rarely encountered neoplasm which may be a surgically amenable cause for epilepsy. MA occurring concurrently with focal cortical dysplasia (FCD) is infrequently described in the literature, which may have implications in regards to extralesional epileptogenicity and poor response to surgical lesionectomy. A staged surgical approach of intracranial implantation may offer a greater opportunity to adequately localize the epileptogenic zone and extend resection margins with preservation of functional tissue.

Methods: A 30 year old female with MA and FCD presented preoperatively with medically intractable epilepsy since the age of 12 and events described as weekly clusters of brief confusional spells associated with hypermotor activity. Radiographic, electrographic, histopathological findings are reviewed in the context of a meta-analysis of the literature. A staged surgical approach with an initial implantation of subdural electrodes to verify lateralization and localization, followed by a larger grid implantation after partial excision of the lesion in order to expand the margins of resection and to allow for functional mapping was performed.

Results: Scalp EEG was remarkable for paroxysmal generalized polyspike discharges, with evolution of non-lateralized frontally predominant generalized fast frequency activity at seizure onset. MRI demonstrated an abnormal frontal gyral pattern, with a calvarial defect and tiny focus of enhancement. PET showed metabolic reductions in the inferobasal temporal lobes and left anterior frontal lobe. The first stage of intracranial monitoring revealed seizures with initial electrographic change over the left frontal region perilesionally with rapid bisynchrony and spread to the left temporal region. Interictal spike wave discharges were observed independently in the left frontal, left temporal, and right frontal lobes. After initial resection of the lesion, subsequent grid implantation and mapping redemonstrated seizure onset from the surrounding tissues, in close approximation to the left frontal language area and motor cortex. Histopathology from the initial resection showed intracortical plaque-like proliferation of meningothelial cells, microvasculature and fibroblast-like cells consistent with MA. Subsequent resection showed pyramidal neurons with apical dendrites oriented in directions other than the pial surface disrupting normal lamination consistent with FCD type IIa. Outcome is Engle class II with 4 seizures at 1 year and substantial functional improvement.

Conclusions: The literature describes variable outcome with local surgical excision with rates of seizure freedom between 43-68%. MA is rarely reported in association with FCD, however extra-lesional and multifocal or generalized electrographic findings have been described. A staged surgical approach with functional mapping may allow for more complete resection of the epileptogenic zone with a lower risk for functional impairment, and should be considered when MA is thought to be the cause of medically refractory epilepsy.

IMAGE: images/904319_A.jpg

T2 MRI sequence demonstrating an abnormal frontal gyral pattern in association with a calvarial defect. FDG PET scan of the brain demonstrating metabolic reduction in the left superior anterior frontal lobe.

IMAGE: images/904319_B.jpg

A. Cortical lesion characterized by a plaque like proliferation of meningothelial and fibroblast-like cells surrounding small blood vessels consistent with meningioangiomatosis. B. Significant number of pyramidal neurons with apical dendrites oriented in directions other than the pial surface disrupting the normal lamination consistent with cortical dysplasia.

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GAMMA KNIFE SURGERY FOR REFRACTORY INSULAR CORTEX EPILEPSY

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Rationale: Work from our group and others have shown that a certain proportion of medically intractable epilepsy patients have an epileptogenic zone that involves the insula. Surgery of the insular region is however associated with non-negligeable risks of injury to the opercula, branches of M2 segment of the middle cerebral artery and deeper structures such as the arcuate fasciculus, internal capsule and basal ganglia . Growing evidence supports the use of gamma knife surgery (GKS) in the treatment of seizure caused by brain tumors, arteriovenous malformations, cavernous hemangiomas and hypothalamic harmatomas. We report our experience with gamma knife surgery for pharmacoresistant insular cortex epilepsy (ICE).

Methods: Retrospective study of all patients with refractory ICE treated by GKS between January 2005 and January 2010. All patients underwent an extensive presurgical evaluation prior to treatment, including video-EEG monitoring, high-resolution structural MRI, ictal SPECT and neuropsychological assessments. Radiosurgical treatment was performed by using a Leksell Gamma Knife 4C (Elekta Instruments AB). Seizure frequency after treatment was assessed and compared to baseline.

Results: Three cases of medically intractable ICE treated by GKS were found (2M/1F). Mean age was 48 (range 38 to 64). Marginal and maximum radiation doses delivered were 20 Gy and 40 Gy, respectively. Treatment volume ranged from 1.2 to 3.2 cc. Case 1 had nonlesional ICE proven by depth insular electrodes but only transiently improved after left posterior insulectomy (Engel 3). Complementary GKS targeting the residual superior portion of the posterior insula led to an Engel 1 outcome after a latency of 15 months (FU = 4yrs). Case 2 had refractory ICE due to a left insular cavernoma. Seizure-freedom was attained 5 months after GKS (FU = 3.5 years) though antiepileptic withdrawal was not possible. Case 3 has refractory ICE associated with a nonspecific millimetric signal abnormality over the left posterior insula. An intracranial study confirmed the insular epileptogenic zone but was complicated by transient dysphasia from contusion of the left superior temporal gyrus. Intracerebral electrodes were removed without resective surgery. GKS was performed only 5 months ago and a longer period of follow-up is required prior to assessing efficacy (outcome at one year will be available at the meeting in December 2010). None of the patients had complications after GKS.

Conclusions: To our knowledge, this is the first series of GKS performed for refractory ICE. Preliminary results indicate that GKS is a safe and promising method to control insular seizures.

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HIPPOCAMPAL TRANSECTION FOR TEMPORAL LOBE EPILEPSY PATIENTS WITH ORGANIC LESIONS AND MRI-NORMAL HIPPOCAMPUS

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Rationale: Hippocampal transection is a newly developed method for the treatment of left temporal lobe epilepsy (TLE) with full preservation of verbal memory. We applied this method to TLE patients with organic lesions and MRI-normal hippocampus.

Methods: The study subjects were four patients with intractable TLE associated with three cavernous angiomas and one dysembryoplastic neuroepithelial tumor. Preoperative examination of each subject demonstrated TLE of the same side same as the organic lesion. MRI showed a normal hippocampus and FDG-PET revealed medial temporal hypometabolism on the side of the focus. After an initial lesionectomy and then, recording of intraoperative electrocorticography (ECoG) was commenced. Multiple transections of the pyramidal layer under the alveolus were performed until the epileptic discharges from the hippocampus were completely abolished. The patients respectively underwent two left-sided and two right-sided surgeries, and were followed up for more than 1 year. The amytal test confirmed left-sided memory dominance in two patients with left-sided lesions. Wechsler Memory Scale Revised (WMS-R) tests were performed at 2 weeks, 6-months, and 1-year after surgery.

Results: 1) All four of the patients obtained seizure-free outcome. 2) Two patients with right-sided transection showed no change in visual memory, verbal memory, and delayed recall at 2 weeks, 6-months, and 1-year after surgery. 3) Two patients with left-sided transection showed marked deterioration of visual memory, verbal memory, and delayed recall at 2 weeks after surgery. All of those models of memory improved gradually and almost returned to preoperative levels by 1 year after surgery.

Conclusions: The results from the present study suggest that hippocampal transection for TLE patients with organic lesions and MRI-normal hippocampus is a useful method for achieving seizure cessation and memory preservation.

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CORRELATION OF SCALP EEG AND MRI FINDINGS WITH OUTCOME OF EXTRAOPERATIVE ELECTROCORTICOGRAPHY IN TEMPORAL LOBE EPILEPSY

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Rationale: Confounding features of scalp EEG (sEEG) ictal patterns (IPs) and interictal epileptiform discharges (IEDs), magnetic resonance (MR) imaging and other nonelectrographic data in temporal lobe

epilepsy (TLE) requires the use of extraoperatvie electrocorticography (eECoG) for further clarification of the ictogenic source. We assessed both electrographic and MR imaging features in cases requiring lateralization by such means.

Methods: An institutional archival review identified adults with a putative TLE who required eECoG with bitemporal electrode placement. According to ictal patterns on sEEG, these patients were categorized into two main groups: I, unilateral (UL) IPs and II, bilateral (BL) IPs. Each group was further subdivided according to IED findings (Table). Patients who proceeded to surgery after eECoG were grouped according to findings on sEEG: I, exclusively concordant ipsilateral (IP) with discordant nonelectrographic data; II, IL preponderant (>75% of IPs); III, contralateral (CL) preponderant (>75% of IPs). The presence of medial temporal sclerosis (MTS) in each group was studied with regard to outcome of eECoG and resection. A favorable seizure outcome was accepted as Engel class II B and above. Descriptive statistics were applied to test for correlation between each of eECoG, sEEG and the presence of MTS and postsurgical outcome.

Results: Twenty-nine patients (14F, 15M) with a mean age of 37y (16-59y) and a mean age at epilepsy onset of 16y (0-32y) were accrued. In the surgery group, the mean age at surgery was 33y (14-52y) and the mean postoperative followup was 37m (7-67m). A unilateral IP on sEEG was found in 22 patients (Group I) and a bilateral IP in 7 (Group II). In Group I, 14/22 (64%) had correctly lateralized IEDs. Of those showing bilateral (6) and generalized (1) IEDs, 5 cases showed a preponderance (>75%) on the epileptogenic side raising the correlative value to 86%. In Group II, IEDs suggested bilateral epileptogenicity in 5/7 (71%) with the remainder showing no IEDs. Lateralization according to eECoG provided reliable outcome prediction ($p<0.001$) for resection (Table). MTS was identified in 10/19 (53%) of the surgery cohort and showed no association with lateralizing IPs or IEDs. Of the 19 cases undergoing resection, 14 (74%) had a favorable outcome including 10 patients who achieved seizure-freedom.

Conclusions: Both interictal and ictal sEEG provide a high yield of correct lateralization in TLE exclusive of the presence of MTS in cases requiring eECoG. There appears to be no correlation with the presence of MTS and sEEG in this study cohort.

Lateralization capability of scalp EEG patterns and the presence of MTS in TLE cases requiring bitemporal eECOG

IMAGE: tables/906774_T1.jpg

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SEIZURE AND NEUROPSYCHOLOGICAL OUTCOME FOLLOWING MESIAL TEMPORAL LOBE EPILEPSY SURGERY: SELECTIVE AMYGDALOHIPPOCAMPECTOMY VS. ANTERIOR TEMPORAL LOBECTOMY

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Rationale: Although surgery has been proven effective in the treatment of pharmacoresistant mesial temporal lobe epilepsy (MTLE), controversy exists regarding the optimal extent of resection for seizure and neuropsychological outcome.

Methods: A retrospective study was performed of all patients who have undergone an anterior temporal lobectomy (ATL) or selective amygdalohippocampectomy (SAH) for MTLE at Notre-Dame Hospital from January 1980 to July 2007. All patients underwent a comprehensive presurgical evaluation including complete neuropsychological testing before and after surgery. Seizure outcome was evaluated using the Engel classification scale.

Results: During the study period, 142 patients underwent temporal lobe surgery for refractory TLE. There were 116 ATL and 26 SAH. In this series, 62% (n=16) of SAH and 61% (n=70) of ATLs were operated on the left side. Hippocampal sclerosis (HS) was diagnosed at pathology in 48% (n=56) of ATL and 85% of SAH (n=22). Patients used an average of 4.4 (range 2-12) antiepileptic drugs before surgery. After a mean follow-up of 4.3 years, a favorable seizure outcome (Engel I and II) was noted in 91.5% and 85% of patients who had undergone ATL and SAH, respectively. However, only 28% of the patients who had undergone ATL and 46% of those who had undergone an SAH were seizure free (Engel Class Ia). Rate of quadranopsia was higher in ATL (31%) than in SAH (12%). Language difficulties occurred in 17% and 12% of patients undergoing ATL and SAH, respectively. Subjective memory impairment rate at office visit was 12% in patients undergoing ATL (n=14) and SAH (n=3). Detailed neuropsychological outcome data is currently being assessed and will be shown at the meeting in December 2010.

Conclusions: These results add to the limited existing data suggesting that long-term seizure outcome is comparable following ATL and SAH for MTLE.

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STATISTICAL MODELING OF ICEEG FEATURES THAT DETERMINE RESECTION PLANNING

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Rationale: The interpretation of ictal intracranial EEG (ICEEG) recordings for resection planning is a complex balance of the significance of specific rhythms (e.g. low voltage fast activity vs. rhythmic slowing) and their relative timing to seizure onset (initial ictal activity vs. later spread). Various interictal findings are also felt to be indicative of the epileptogenic zone. Ictal and interictal findings are then evaluated in light of findings from cortical stimulation of eloquent cortex to determine the area of resection. We describe factors involved in resection planning by statistically analyzing features that led to inclusion of an electrode in the resection map.

Methods: Patients from April 2009 through May 2010 with ICEEG grid electrodes and subsequent surgical resection were retrospectively identified. The epileptologist who managed each case reviewed the ICEEG record noting ictal and interictal findings specific to each electrode. Only the first 15 seconds of ictal activity, which was divided into five 3-second epochs, was considered. The epoch in which each electrode became active and the pattern of activity observed at that time were recorded for each electrode. The descriptors used to codify the ictal and interictal EEG features are listed in Table 1. If multiple seizure types were seen in a single patient, a representative seizure was described for each type and weighted based on the proportion of that

patient's seizures it represented. The presence of eloquent cortex or a known lesion under each electrode was noted as well. Every electrode in each patient was considered a separate observation in a logistic regression model to predict whether the cortex under a given electrode was included in the planned resection.

Results: The 19 patients had a total of 37 unique seizures. Recordings from a total of 1306 electrodes were analyzed with results of the logistic regression analysis noted in Table 1. The strongest predictors of resection of cortex underlying a given electrode was presence of low-voltage fast activity in Epoch 1 (first three seconds of ictal activity), rhythmic spikes in Epoch 1, interictal paroxysmal fast activity, and low-voltage fast activity in Epoch 2. High-amplitude beta spikes and rhythmic slow waves were also significant predictors in Epoch 1, but were not significant in later epochs. Interictal spikes had a higher odds ratio of affecting the planned resection if described as "continuous" or "very frequent", but less frequent spikes were also significant predictors. The presence of motor or language cortex were the strongest negative predictors of resecting underlying cortex, however eloquent sensory cortex was not found to be significant.

Conclusions: Early low voltage fast activity and rhythmic spikes were the ictal rhythms that most strongly indicated the need for resection, but interictal paroxysmal fast activity was an equally strong predictor. Motor and language cortex were the strongest negative predictors for inclusion in the planned resection. The presence of sensory cortex was not a significant predictor.

Ictal and Interictal Electrode Observations

IMAGE: tables/902855_T1.jpg

(*) = Clinically Significant at á d" 0.05

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LONG TERM EFFICACY OF THE SANTE TRIAL (STIMULATION OF THE ANTERIOR NUCLEUS OF THALAMUS FOR EPILEPSY)

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Rationale: Fisher et al.(Epilepsia,51:899,2010),reported the results of 110 patients who participated in a multicenter, double-blind, randomized controlled trial of bilateral stimulation of the anterior nuclei of the thalamus for localization-related epilepsy, and found benefit that persisted through 2 years.This is a preliminary report of the efficacy for 42 patients with at least 3 years stimulation. Data for all patients will be presented at the AES.

Methods: subjects were 18-65 years old with at least 6 partial or secondarily generalized seizures per month, and who had failed at least three AEDs. Patients with IQ < 70, inability to complete neuropsychological testing or progressive neurological lesions were excluded. The trial utilized a prospective, randomized, double blind, parallel group design. After a 3-month baseline, deep brain stimulation (DBS) electrodes were implanted in the AN bilaterally using a stereotactic technique. One month after implantation, subjects were randomized to stimulation at 5V or no stimulation. After 3 months of blinded treatment, all received stimulation; limited stimulation changes were allowed. Long term follow-up began at 13 months with stimulation parameters adjusted at the investigators' discretion. Primary analysis was performed on subjects with at least 70 days of seizure data.

Results: DBS therapy reduced the number of seizures in a very refractory patient population, with a median seizure frequency reduction of 40% by the end of the blinded phase (vs.14.5% for control). There was continuous efficacy improvement; the median percent reduction from baseline at one year was 41%, at 2 years was 56% and at 3 years was 68%. The responder rates (>=50% reduction in seizure frequency) also improved over time; at one year the responder rate was 43%, 54% at 2 years and 67% at 3 years. Over the entire study 13% of subjects were seizure-free for at least 6 months, and 4 subjects were seizure- free for over 2 years. There were no unanticipated adverse device effects, and no symptomatic intracranial hemorrhages. The Liverpool seizure severity scale and quality of life measure (QOLIE-31) also showed statistically significant improvement over base line by one year, which continued to be significant at 2 and 3 years ($p<0.001$). Neuropsychological profiles remained stable.

Conclusions: Long term follow-up of bilateral stimulation of the anterior nuclei of the thalamus, showed sustained efficacy and continuous improvement, with a median percent reduction in seizure frequency of 68% at 3 years. Deep brain stimulation of the thalamus is helpful for some people with medically refractory partial and secondarily generalized seizures

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TEMPORAL LOBE EPILEPSY SURGERY IN CHILDREN: CONSIDERATIONS FOR PROGNOSTIC PREDICTORS

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Rationale: Many reports demonstrate the possibility of favorable outcome following temporal lobe epilepsy surgery. Data varies by center, but seizure freedom or significant reduction in seizure frequency is reported previously. We aim to review the outcome data in our institution for temporal lobe epilepsy surgery in younger age (less than 20 years of age) in order to determine indicators for favorable outcome.

Methods: We retrospectively reviewed the epilepsy surgery data base who underwent temporal lobe resection due to intractable epilepsy between 1992 and 2009 at the Medical College of Georgia. We examined demographic data, clinical history, EEG, MRI, neuropathology, and follow up at 1, 3 and 5 years with Engle classification. We focused the analysis on resection types and tissue diagnosis by postsurgical neuropathological examination. Surgical types were categorized as anterior temporal lobectomy (TL), lesionectomy (Le), amygdalohippocampectomy (AH), and temporal lobectomy with sparing of the hippocampus (TLwo). Pathology was categorized as mesial temporal sclerosis (MTS), cortical dysplasia (CD), gliosis (G), tumor (T) and dual pathology (D). Statistical analysis was done by ANCOVA.

Results: Ninety cases (mean age, 12.9 years; range 0.5 and 20 years of age) were included; 51 males, 39 females. Of the 90 cases (Lt 52, Rt 38), there were 64 TL, 14 TLwo, 8 Le, and 4 AH. Combining all surgical types, good outcome (Engel I or II) was achieved in 94.4% (85/90) at one year, 87.8% (72/82) at year three, and 81.7% (49/60) at year five follow up. Separate analysis of the surgical types reveals better outcome in the TL group with good outcome in 98% (63/64) at one

year, 91.5% (54/59) at 3 year, and 83.3% (40/48) at five year. In contrast, poorer outcome was observed in the TLwo group (Lt 11, Rt 3) with good outcome being achieved in 78.6% (11/14) at one year, falling to 69% (9/13) at three year, and to 67% (4/6) at five year follow up (p=0.09). Thirty one (34%, Lt 22, Rt 9) of the patients required invasive monitoring with depth electrode and grid placement prior to resective surgery. Reviewing pathology, 28 patients had MTS, 16 with cortical dysplasia, 9 with tumors, 14 with gliosis, and 23 with dual pathology. Those with MTS had the best outcome with persistent benefit, 100% (28/28) good outcome at 1 year, 96% (26/27) at 3 year, and 95% (20/21) at 5 year. The presence of gliosis indicated a propensity to lose seizure control over time, with 1 year good outcome in 92% (13/14). However, at 3, 5 years, the benefit dropped to 70% (7/10) and 62.5% (5/8) respectively. A similar trend was noted in dual pathology as well as cortical dysplasia (p=0.14).

Conclusions: We conclude that TL with the presence of MTS has the favorable outcome with sustained benefit. The poor outcome was observed in patients with TLwo. The presence of MTS has tendency of the better outcome while gliosis offers a poorer predictive outcome.

2.271

DOES MULTIMODALITY IMAGING CONTRIBUTE TO MANAGEMENT OF PHARMACO-RESISTANT EPILEPSY IN CHILDREN WITH TUBEROUS SCLEROSIS COMPLEX?

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Rationale: Seizure control is known to be the best indicator to determine Tuberous Sclerosis Complex (TSC) patients' overall developmental outcome and quality of life. Conventionally, favorable surgical outcome in TSC is associated with concordance between scalp EEG and dominant MRI tuber(s). We studied the usefulness of multimodality imaging tests in identifying surgical candidates and in improving surgical outcome in tuberous sclerosis complex (TSC) patients.

Methods: We retrospectively reviewed 21 patients with TSC who underwent resective surgery (8 M/ 13 F, aged 1 - 27 years, mean 7.3) following pre-surgical evaluation. Patients were classified into "conventional" and "challenging" candidate groups based on concordance between the dominant tuber on MRI and the ictal onset zone on scalp EEG. Clinical characteristics, type of surgery, surgical outcome and localizing features on non-invasive pre-surgical evaluation including MRI, scalp EEG, SISCOM, SPM analysis of FDG-PET and MEG/MSI were reviewed.

Results: Overall seizure-free outcome in 21 patients was 57% (12/21). Out of 21 patients, only ten (48%) were initially classified as conventional candidates following MRI and video scalp EEG. Additional 11 patients were recommended surgery with the help of multi-modality tests. The seizure-free outcome of the challenging candidates (55%, 6/11) was similar to that of the conventional candidates (60%, 6/10). There was no difference in each test's concordance with intracranial EEG: SISCOM 7/12 (58%), SPM-PET 10/19 (53%) and MEG 8/16 (50%). In conventional candidates, seizure-free outcome tended to be higher in the patients whose SISCOM (75%, 3/4), SPM-PET (67%, 4/6) or MEG (100%, 4/4) was concordant with intracranial EEG than the group's average outcome (60%). In challenging group, surgical outcome was tended to be higher in the patients whose SISCOM (67%, 2/3) or SPM-PET (67%, 4/6) showed concordance with ictal EEG than the group's average (55%).

Conclusions: Our data suggest that multimodality imaging contributes mainly through expanding surgical candidacy in TSC patients. Large multi-center study may be necessary to see whether multi-modality tests truly contribute to the improved surgical outcome.

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VAGUS NERVE STIMULATION (VNS) IN CHILDREN WITH REFRACTORY SECONDARY GENERALIZED OR MULTIFOCAL EPILEPSY WHO WERE NOT CANDIDATES FOR CORTICAL RESECTION

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Rationale: VNS has been used to treat focal and generalized epilepsy in both adults and children. Over the last years, we have tried to investigate more homogeneous patient populations that would get better results from VNS treatment. We report data from an on-going prospective study that offered VNS therapy to children with refractory secondary generalized or multifocal epilepsy who were usual candidates for callosotomy at our institution.

Methods: Twenty-three kids under the age of 12 were included so far (mean= 8.4 years). Fifteent had secondary generalized (Lennox and Lennox-like syndromes) and 8 had multifocal epilepsy with generalized cortical abnormalities (tuberous sclerosis, double cortex syndrome, post-encephalitis). All were submitted to VNS. Final standard parameters were 2.5 mA, 500usec and 30Hz (30 sec "on", 5 minutes "off"), with progressive 0.25 mA increments every 2 weeks. Families kept a full seizure diary and neuropsychological and quality of life assessments were performed every 6 months. Mean follow-up so far is 8.6 months.

Results: One kid developed stimulation-related Parkinsonism and VNS was discontinued despite a dramatic decrease in seizure frequency (80%) during therapy. The other 22 patients got at least 50% seizure frequency reduction. Seizure frequency decrease was initially noted when stimulation reached 1 mA in all patients. Attention level and cognitive improvement was noted in every kid, and did not strictly correlate with seizure outcome. All families considered that VNS had benefited their children so far. There was an immediately postoperative period (generator "off") of seizure frequency reduction ("honeymoon phase") in 10 patients, which lasted 2-3 weeks. Four kids presented seizure frequency worsening when stimulation current was set higher then 2.5 mA.

Conclusions: This patient population appeared to represent a set of patients with better seizure and cognitive outcome after VNS. Seizure frequency reduction was noted with stimulation parameters lower (1 mA) than those needed in adults and earlier during treatment. As noted with other epilepsy surgery procedures, a "honeymoon phase" was noted. Children might be at higher risk for seizure frequency worsening at higher stimulation currents when compared to adults.

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INVASIVE INTRACRANIAL MONITORING IN PEDIATRIC EPILEPSY SURGERY:WHEN USEFUL AND WHEN NOT

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Rationale: Indications for invasive subdural monitoring in pediatric epilepsy surgery are poorly defined.We sought to critically review our experience with pediatric invasive intracranial monitoring to better delineate when invasive EEG is useful.

Methods: Patients who had subdural invasive EEG monitoring for epilepsy surgery were identified from an epilepsy surgery database at Miami Children's Hospital Brain Institute. Exclusion criteria were inadequate subdural data and children with infantile spasms/myoclonic epilepsy. Pre-invasive evaluations were retrospectively reviewed including history, interictal/ictal scalp EEG,MRI and functional imaging in selected cases. Indications for subdural implantation were categorized based on pre-invasive data as :1) Mapping of eloquent cortex 2) Poorly localized epileptogenic zone(EZ)3) Discordant data.Subdural EEG reports,surgical diagrams and functional mapping were reviewed for localization of the EZ and compared with pre-invasive data for congruence. Data on surgical resection, completeness, complications and outcome were analyzed.

Results: 102 patients met inclusion criteria.12 were implanted for mapping eloquent cortex,76 for non-localized EZ and 14 for divergent data. In the non-localized group 45% had negative MRIs. A focal area for resection was identified in 99%(68% incomplete). Subdural monitoring impacted resection in 84%. Implantation for functional mapping facilitated incomplete resections in 42% due to proximity to eloquent cortex. Of cases implanted solely for language mapping in a presumed dominant hemisphere,5 were redundant as all underwent anterior left temporal lobectomy. Implantations to determine the extent of involvement beyond the mesial/anterior temporal region were rarely useful particularly if there was a focal MRI lesion.90% resulted in anterior temporal lobectomies. Most poorly localized cases were multilobar (paracentral n=21, frontotemporal n=15, posterior quadrant n=9,other multilobar n=15). 1 paracentral case resulted in explantation.The EZ was outside motor cortex in 38% and only partially overlapped motor in several cases resulting in 5 complete resections. Frontotemporal implantations resulted in lobar resections in 73%. Posterior quadrant and other multilobar implantations usually resulted in more restricted resections than anticipated by non-invasive data(79%)and no quadrantectomies. 14 cases were implanted for discordant data with 13 resolving the discordance. With divergent scalp EEG and MRI subdural EEG more often was concordant with MRI than scalp EEG(71% vs 28%).

Conclusions: There is limited pediatric data guiding the use of intracranial monitoring to localize an epileptogenic focus for resective surgery. This study provides an overview of current indications at an active pediatric epilepsy surgery centre and examines the utility of those practices. We confirmed the adult experience that subdural monitoring is rarely helpful for MRI-lesional temporal lobe epilepsy. Routine use of functional neuroimaging modalities may obviate the need for many invasive cases previously deemed poorly localized.

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SURGICAL EFFICACY AND SAFETY IN MULTILOBAR PEDIATRIC EPILEPSY

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Rationale: To demonstrate the safety and efficacy of surgical management in multilobar pediatric epilepsy with subhemispheric involvement. The prognosis for seizure freedom is thought to be poorer in the setting of several epileptogenic zones involving multiple lobes, where hemispherectomy is contraindicated. We describe 16 patients whose age, language or sensorimotor capabilities precluded hemispherectomy, who underwent multilobar resections and disconnections in the setting of medically intractable seizures.

Methods: 13 children and three adults, aged 15 months to 46 years, with medically intractable epilepsy since childhood, were followed at the Comprehensive Pediatric Epilepsy Center at Beth Israel Medical Center in New York. Pre- and post-operative evaluations included EEG recordings with video monitoring, MRIs, PET scans, and functional MRIs. All patients were treated with staged operations spaced by at least one week, using invasive monitoring and functional mapping with grid and strip electrodes. Pre-operative MRI findings included perinatal infarction, post-traumatic encephalomalacia, cortical dysplasia, mesial temporal sclerosis and a treated arachnoid cyst. All patients experienced disabling complex partial seizures and impediments of language, social, academic and motor development.

Results: Ten children underwent a combination of anatomic and functional posterior quadrantectomy. In three of these patients, a partial frontal resection accompanied the quadrantectomy. One child with a dominant hemisphere perinatal parieto-occipital stroke underwent a temporal and occipital resection. The remaining six patients had combined temporal and frontal resections. Language and sensorimotor functions were preserved in all cases. All patients have Engel I outcomes (10 Engel 1A, 2 each of Engel IB, IC, ID) with follow up ranging from 3 months to 3 years.

Conclusions: Children and adults with multilobar epilepsy due to multiple pathogenic mechanisms, who are not candidates for hemispherectomy, can be safely and effectively treated with epilepsy surgery. Staged operations with invasive mapping are necessary to comprehensively delineate the epileptogenic zones and distinguish them from functional areas.

IMAGE: images/904823_A.jpg

The epileptogenic zone is delineated by the black line in this 12 yo with a perinatal watershed infarct of the right parietal lobe. Lateral temporal, occipital, and parietal cortices were involved in seizure onsets. Numbers 1-5 correspond to sensory cortex.

IMAGE: images/904823_B.jpg

The same patient in Figure 1 is presented here after subhemispheric multilobar resection and disconnection. Intraoperative photo demonstrating lateral temporal lobectomy and parieto-occipital disconnection, sparing the sensory cortex. The hippocampus is visible in the mesial temporal lobe.The patient is seizure free (Engel IA) at 3 years F/U and had a marked improvement in cognitive abilities after surgery.

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FUNCTIONAL CONSEQUENCES AND MORBIDITY OF HEMISPHEROTOMY

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Rationale: Hemispherotomy (HP) has been performed successfully in treatment of epilepsy, with similar prognosis but less morbidity than hemispherectomy. The optimal timing for surgery tends to be retarded since it is still considered the most radical surgical procedure, resulting in definitive deficits. This study reports pre-, intra- and post-operative (PO) data to better evaluate morbidity and functional consequences of HP.

Methods: A retrospective study included 12 children (8 boys, age 1.3-13.5 years) with unilateral hemispheric diseases and pharmacoresistant seizures, who underwent HP at Hospital São Paulo between 2003-2010. All had been assessed using a standard protocol involving clinical, neurophysiological and neuroradiological evaluation. Clinical information was selected to survey presurgical and operative variables, including PO seizure control and pre- and post-surgery language and motor functions. Functional level of each child was evaluated through Gross Motor Function Classification System (GMFCS) and Manual Ability Classification System (MACS), which classify the child's movement and manual abilities, respectively. Data were analyzed using a statistical program (SPSS for Windows®); level of significance was $p < 0.05$.

Results: The underlying pathology was Rasmussen encephalitis in 6 patients (50%), ischemic insult in 5 (42%) and hemimegalencephaly in 1 (8%). Left hemisphere was involved in 9 (75%). Seizure onset ranged from 0.2 to 7.4 years (3.4), lasting from 0.1 to 11 years (mean 2.4). The mean duration of surgical procedure was 9.8 hours (8-15); of orotracheal intubation, 26.4 hours (10-48); of ICU and hospital stay, 2.5 (1-5) and 10.8 (5-18), respectively. One child presented intraoperative and all patients had PO mild or moderate reversible complications, such as hypertension, bleeding, ventriculitis, insipidus diabetes, atelectasis, trigeminal neuralgia, seizures and fever. The PO follow-up period ranged from 0.2 to 7 years (mean 2.4). Five/12 were classified in Engel's classes I or II at 2 years and 8 (67%) in Engel I, 2 Engel II and 2 Engel III at the last follow-up. In the latter two patients epilepsy duration was longer than 10 years ($p=0.02$). Prior to surgery, all children exhibited hemiparesis (from I to IV); 9 were functionally independent being 4 (33%) GMFCS I and 5 (42%), GMFCS II. Nine of these children were GMFCS II at PO period. Three were III and V prior to surgery and remained so afterwards; these patients presented the earliest seizure onsets (0.2 and 0.5 years). Before surgery, fine finger movement was preserved in 6 children; 5 who were MACS I turned to II at PO evaluation, with maintenance of functional manual ability. Of the 9 children with language skills, they remained unchanged or even improved in all, including 6 (67%) who had left-side resection. Four (44%) of these children were older than 6 years at surgery.

Conclusions: HP was a well tolerated procedure, with mild to moderate and reversible complications, effective seizure control and no motor or language strong functional impact. These consequences might help in the process of decision making.

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PROPOSED MULTI-AXIAL CLASSIFICATION FOR OUTCOME OF EPILEPSY SURGERY IN CHILDREN

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Rationale: The most commonly used classification of outcome for epilepsy surgery, the Modified Engel Scale, focuses largely on seizure frequency in determining whether or not surgery produced favorable results. It has been validated in adolescents and adults. The context of epilepsy surgery is different in the pediatric setting, however. Children differ from adults in the distributions of seizure types, onset, and localization. In addition, in catastrophic pediatric epilepsy, seizure freedom is only one goal of surgery. Often, improved quality of life of the patient and his or her family, as well as the hope of improved development, are unspoken goals of surgery. Because of the nature of certain catastrophic epilepsies of infancy (e.g, hemimegalencephaly) and plasticity of the infant brain, the risk-benefit ratio of operating in eloquent cortex is also different. The current use of the Engel system does not encompass these aspects of surgery and a more detailed approach to classification of surgical outcome is necessary.

Methods: We propose a multiple axis approach to classification of outcome that includes outcome scores based on Seizure Freedom (1- Seizure free; 2 = Auras only; 3 = > 90 % reduction in seizure frequency; 4 = 50-90% reduction; 5= < 50% reduction; 6 = No change or increase); Neurological Outcome (a = improvement; b = no change; c= new non-disabling deficit or non-disabling increase in longstanding deficit; d = new disabling deficit) and Quality of Life (+ = improved QOL; nc = no change; - = worse QOL). Institution of this classification scheme requires minimal changes in current pre- and post-surgical evaluations of patients that include seizure monitoring and seizure diaries, standard neurologic examination, and administration of age-specific quality of life measures. As part of our clinical practice, we routinely administer the Quality of Life in Children with Epilepsy Scale at pre- and post-surgical neuropsychological evaluation. Standardized measures of intellectual and neuropsychological functioning are used to assess cognitive and behavioral outcomes.

Results: In 2008, we started using a Pediatric Epilepsy Surgery Outcome Scale (PESO) at one-year post-surgical follow-up evaluations. In comparison to their Engel ratings, patients' ratings on this scale were more variable, as expected, given the greater number of dimensions, and provided more information. No significant delay in pre- or post-surgical assessments of our patients resulted from the inclusion of these measures in our clinics. Of the 6 patients where pre and 1-year post-operative QOL measures were available, no decline in QOL was seen, even in those who sustained a new (expected) neurological deficit (Neurological Outcome = d) or in those who were not seizure-free (Seizure Freedom <1).

Conclusions: A multi-axial approach to the assessment of surgical outcome in children with epilepsy is needed to better characterize all important determinants of results of surgical management in infants and children with refractory epilepsy. Validation studies of the PESO are planned.

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LOCALIZATION OF INTERICTAL NEUROMAGNETIC SPIKE-LOCKED HIGH FREQUENCY OSCILLATIONS (40-120 HZ) IN PEDIATRIC INTRACTABLE EXTRATEMPORAL EPILEPSY

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Rationale: Rationale: High frequency oscillations (HFOs) are often recorded from implanted intracranial electrodes and occur at the time of interictal spikes. The spatial distribution of these HFOs shows strong correlation with the epileptogenic zone. Magnetoencephalography (MEG) is being increasingly used in the pre surgical evaluation of intractable epilepsy. Clinical MEG analysis routinely utilizes the equivalent current dipole model (ECD). As it is affected by the signal to noise ratio, the ECD model will not be suitable for analysis of low amplitude HFOs of interictal spikes. We utilized an event related beamformer (ERB) (Cheyne et al., 2007) to localize interictal spike-locked oscillations (40-120 Hz) and compared the localization accuracy of the ERB to the epileptogenic onset zone identified by intracranial EEG.

Methods: Methods: MEG recordings were performed utilizing whole head 151-channel axial gradiometer system (VSM MedTech). A Minimum of 15 two-minutes data sets were collected with a sampling rate of 625 Hz/1250 Hz. MEG data were inspected at the 3-70 Hz band to mark earliest peaks of MEG interictal spikes. We subsequently applied a band bass filter of 40-120 Hz. We excluded spikes in which gamma and beta oscillations were seen only in the context of generalized discharges or if no 40-120 Hz oscillations were seen in the earliest phase of the spike. We localized the sources of individual interictal spikes utilizing an event-related beamformer. We compared the beamformer source localization to the ictal onset zone identified in intracranial EEGs.

Results: Results: We identified spike-locked oscillations (40-120Hz) in 19 patients with extratemporal intractable pediatric epilepsy. Eighteen patients underwent surgical resection. Surgical resections involved the rolandic cortex in 11 patients, Frontal lobe in four patients, Occipital resection in two patients and hemispherectomy in one patient. One patient declined surgery. Beamformer localization was concordant with the intracranial monitoring results in 18 patients aand was discordant in one patient with tuberous sclerosis.

Conclusions: Beamformer source localization of spike-locked 40-120 Hz oscillations shows strong correlations with the ictal onset zone as identified by intracranial EEGs in a subset of cases of pediatric extratemporal lobe epilepsy.

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PREVALENCE AND PREDICTORS OF DELAYED INTRACTABILITY IN CHILDREN UNDERGOING RESECTIVE EPILEPSY SURGERY

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Rationale: The goals of this study of children undergoing resective surgery for intractable epilepsy were to determine: (1) the proportion of children who achieved a remission of six months or longer in the first year after diagnosis of epilepsy (delayed intractability), and (2) factors associated with delayed intractability.

Methods: All children (0-18 yrs) undergoing respective surgery for intractable epilepsy between January 2002 and May 2010 at Mayo Clinic Rochester were identified by review of the pediatric neurosurgical database. Demographic and epilepsy-related details were obtained through retrospective review of all outpatient and inpatient medical records. The course of epilepsy in the first year after diagnosis was subdivided into two groups: (1) delayed intractability, defined as remission of e"6 months in the first year and failure of no more than one AED in the first year for lack of efficacy, or (2) refractory from onset, defined as no remission of e"6 months or failure of two or more AEDs in the first year for lack of efficacy. Potential factors associated with delayed intractability including age at onset, febrile seizures, history of status epilepticus, cognitive delay, secondarily generalized seizures, abnormal MRI, abnormal EEG, temporal lobe onset, and pathology were evaluated by Chi square and paired t analyses.

Results: Eighty-five children were identified (61% male, mean age at afebrile seizure onset 59 months, mean age at surgery 127 months). Nineteen (22%) achieved a remission of six months or longer within the first year before developing delayed intractability (mean duration of remission 35.3 months, SD 30, range 6-99). A history of febrile seizures was significantly more prevalent in the group with delayed intractability ($p<0.008$). There were also non-significant trends for a history of status epilepticus and normal EEG background to correlate with delayed intractability ($p=0.05$, and $p=0.07$, respectively). The remaining factors, including mesial temporal sclerosis or hippocampal gliosis, showed no significant correlation with delayed intractability.

Conclusions: In this cohort of children undergoing resective surgery for intractable epilepsy, 22% achieved a six month or longer remission in the first year, with the mean duration of remission being approximately three years. These findings suggest that intractability in children with epilepsy may be difficult to predict within the first year.

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SUBTOTAL HEMISPHERECTOMY SPARING THE PRIMARY SENSORIMOTOR REGION (PSMR) - AN ALTERNATIVE TO HEMISPHEROTOMY IN CHILDREN WITH HEMISPHERIC EPILEPSY WITHOUT HEMIPARESIS?

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Rationale: It is well established that for children with a pre-exising hemiparesis, who are suffering from an intractable focal epilepsy, which is caused by a hemispheric pathology, a so-called hemispherotomy is an appropriate and most of the time very successful surgical treatment. In children with severe epilepsy, who do not have a hemiparesis, but are also suspected to have a hemispheric pathology, the decision to perform a hemispherotormy is extremely difficult, because the price these children would have to pay for a good outcome, would be a spastic hemiparesis. Under these circumstances a subtotal hemispherectomy sparing the primary sensory-motor area (pSMR) could be considered as a surgical option, if reasonable results can be achieved by this procedure.

Methods: Retrospective evaluation of the data (neurological status, seizure-semiology, ictal and interictal EEG, imaging data, neuropathology) of 18 patients (11 girls, 7 boys- average age at operation 1 11/12 years, at operation 8 6/12 years) (from a total of 299 patients operated on between 1998 and 2009 at the Epilepsy Center Vogtareuth), who underwent a subtotal hemispherectomy sparing the pSMR - with variable extensions of the areas surrounding the central sensori-motor area. Prior to surgery, only one patient was mentally normal, 4 were moderately, 10 were severely mentally retarded, for 3 there were no test-results available.

Etiology: cortical dysplasia type I 11/18, mild malformation of cortical development 2/18, phacomatosis 3/18, polymicrogyria 1/18, porencephalic lesion 1/18.

Results: Seizure-outcome (Engel's classificaton):

Class Ia 6/18 (33,3%), Class IIb 1/18 (5,6%), Class III a 6/18 (33,3 %), Class IV a/b 3/18 (16,7%).

There is a tendency for a better seizure-outcome in patients, who have been operated on more recently in comparison to patients, who were operated on during the earlier years.

About one third of the patients (from the earlier series)became hemiparetic by surgery because of infarctions.

In the majority of cases improvement in terms of cognition and behaviour was documented; none had a cognitive decline.

Conclusions: There is a significant sub-population of children with hemispheric epileptogenic lesions (predominantly in children with diffuce cortical dysplasia type I), who do not present a hemiparesis. Our data show a favourable post-operative seizure-outcome in more than one third of these patiens after a subtotal hemispherotomy sparing the pSMR. Selection-criteria for this surgical procedure(besides the neurological status) include seizure-semiology, ictal and interictal EEG and neuroimaging data - and the parents' understanding of the complexity of the condition.

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LONGITUDINAL ANALYSES OF THE SURGICAL OUTCOMES OF PEDIATRIC EPILEPSY PATIENTS WITH FOCAL CORTICAL DYSPLASIA

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Rationale: The long-term surgical outcome of pediatric epilepsy patients with focal cortical dysplasia (FCD) is not clear. Here, we report on the long-term surgical outcomes of children with FCD, based on longitudinal analyses.

Methods: We analyzed retrospectively the records of 41 children who received epilepsy surgery for pathologically proven FCD. Twenty patients were male and 21 patients were female. The median age at surgery was nine years (range, 1-17 years).

Results: The actuarial seizure-free rates were 49%, 44%, and 33% in the first, second, and fifth year after surgery, respectively. There was no seizure recurrence after three years. Three patients with initial seizure-control failure experienced late remission of seizures (a running-down phenomenon). Eventually, 19 patients (46%) were seizure-free at their last follow-ups. Absence of a lesion on MRI and incomplete resection were significantly associated with seizure-control failure. Concordance of presurgical evaluation data was an marginally significant variable for seizure control in patients with lesional epilepsy. Three patients with seizure-control failure became seizure-free by the running-down phenomenon. The actuarial rate of antiepileptic drug discontinuation was 91% in the fifth year in the seizure-free patients.

Conclusions: The seizure-free rate after surgery in children with FCD was 49% in the first year; however, it declined thereafter. The running-down phenomenon could be an important mechanism of seizure alleviation for FCD patients during long-term follow-up. As a complete resection of FCD has a strong prognostic implication for seizure control, a better method to define the extent of FCD is required to assist with surgical resection, especially in nonlesional epilepsy.

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EFFECT OF HEMISPHERECTOMY ON CONTRALATERAL SPIKES

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Rationale: Hemispherectomy has been utilized in intractable epilepsy, for seizure reduction or seizure freedom, and has been shown as most effective for seizure control, optimally for lateralized lesions affecting one hemisphere. The goal of the procedure has been seizure control, while the effect on interictal epileptiform activity has not been well studied. Frequent epileptiform activity such as in ESES (electrical status epilepticus during slow wave sleep), causes significant cognitive dysfunction even in the absence of seizures. In such severe cases, interictal epileptiform activity may also be a potential target for therapeutic intervention; in such case, the benefits of hemispherectomy may potentially extend beyond seizure control, by improving cognition through decreasing interictal spikes in the contralateral hemisphere.

Methods: We retrospectively studied consecutive 24 patients with hemispherectomy (anatomical (13) and functional (11), from 1995-2010, through our internal database, which was approved by our institutional review board. All patients had clinical care at Children's Hospital Boston. Clinical data including demographics, interictal and ictal EEG, MRI and pathological data were analyzed. EEG findings including interictal spike distribution and frequency were compared, before and after hemispherectomy.

Results: Clinical Data:

Age of hemispherectomy ranged from 6 months to 12 years (mean 5.5+/-4.2 years). Pathology was diverse, including structural and functional lesions (malformations of cortical development including cortical dysplasia and hemimegalencephaly (9), perinatal stroke (3), traumatic brain injury (1), auto immune encephalitis (1), viral encephalitis (1) and of unknown etiology (1). All patients had intractable epilepsy failing multiple antiepileptic drugs (mean 2.5+/-1.2 drugs).

EEG data:

16 patients had bilateral spikes seen on pre-surgical EEG. 12 out of the 16 patients, including 3 who had ESES, had complete abolition of spikes in the contralateral hemisphere on follow-up EEG (obtained 1-3 months after hemispherectomy). Remaining 4 had no change in the

contralateral spikes. None of the patients showed worsening of their spike count, cognitive symptoms, or seizures. All showed improvement in quality of life. Out of the 12 patients who had complete abolition of spikes, 7 had anatomical hemispherectomy and 5 had functional hemispherectomy; thus procedure type did not influence outcome in spike reduction.

Conclusions: From our data, we showed that hemispherectomy in intractable epilepsy with spikes in bilateral hemispheres, resulted in complete abolition of spikes in most cases (12 out of 16), regardless of etiology and age at surgery. From our results, we suggest that presence of epileptiform activity in bilateral hemispheres including ESES is not a contraindication for hemispherectomy; in fact, there may be advantages for improving function of the contralateral hemisphere by reducing potential epileptic and epileptiform encephalopathy from the interictal spikes.

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EARLY SURGICAL TREATMENT OF EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY / OHTAHARA SYNDROME

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Rationale: Early Infantile Epileptic Encephalopathy (EIEE) has a bad prognosis. Seizures almost never respond to medical treatment, psychomotor development is severely impaired, mortality is high. There are a few case reports of surgical treatment only after months of medical treatment failure. Seizure control and development improved after these surgeries. Realizing that medical treatment has failed to produce a good outcome, we recommended and performed surgery as soon as possible for infants with unilateral developmental cortical abnormalities and EIEE. We report our experience with 3 infants who have undergone early surgical treatment.

Methods: Two girls, 1 boy, all had tonic spasms in clusters, 150 to over 300 / day, who met diagnostic criteria for EIEE underwent early surgery. While being evaluated for surgery, they received medical treatment with little benefit (table 1). All 3 infants had a modified hemispherectomy with removal of the pre-M1, subcollosal gyri and the insula.

Results: All 3 are seizure free since surgery and have improved development. Patients 1 and 3 have fraternal twins. Parents report that they are now behaving similar to their twin and development has almost "caught up".

All three have hemianopsia and prefer to use the hand contralateral to the good hemisphere. Surprisingly, all three have finger flexion-extension grip and release, and independent movement of fingers in the hand contralateral to the hemispherectomy. Postoperative EEG shows a normal wake and sleep pattern over the good hemisphere and a less well organized suppression-burst pattern over the remaining hemispherectomy side. Pathology shows cortical dysplasia in all three.

Conclusions: Early surgical treatment of EIEE in selected cases has been effective for seizure control, improvement in alertness, and development. Although it is too soon and these infants are too young to predict ultimate developmental outcome, they appear to be much better than when they were having 200 or more clinical seizures per day and suffering from continuous electrographic epileptic encephalopathy. The use of the fingers on the hand contralateral to the hemispherectomy is an unexpected benefit.

Demographics / Presurgical Testing

IMAGE: tables/907530_T1.jpg

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VAGUS NERVE STIMULATION FOR MEDICALLY REFRACTORY EPILEPSY IN THE PEDIATRIC POPULATION

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Rationale: Treatment for pediatric patients with medically refractory epilepsy always needs multimodal strategies including ketogenic diet, focus resection or disconnection by cranial surgery, or vagus nerve stimulation (VNS). VNS has been well recognized as one of the treatment options for palliation. When VNS was approved by the FDA in 1997, VNS was indicated for adult and adolescent patients 12 years and older with medically refractory partial onset seizures. However, its use for young children is widely accepted at present. An investigation regarding its indications, effectiveness in seizure control, and safety of VNS in the pediatric population was carried out to establish therapeutic strategy for medically refractory epilepsy focused on VNS in children.

Methods: Seventy consecutive pediatric patients (38 girls and 32 boys) 15 years and younger (mean age 9.3 years, range 3-15 years) underwent an implantation of the VNS Therapy System (Cyberonics, Inc., Houston, TX) for the treatment of medically refractory epilepsy and were followed up at the NYU Comprehensive Epilepsy Center. The exact indications for VNS, long-term outcome in terms of seizure reduction and complications by the treatment with VNS particularly in children were analyzed retrospectively.

Results: Fifty-one patients were treated only with VNS, and 19 other patients were treated by combination with VNS and cranial surgery such as resection and/or disconnection. Most of the reasons why VNS was chosen for the treatment were that cranial surgery was not an appropriate option because patients had intractable generalized (40%) or multifocal epilepsy (40%), and failed cranial surgery (17%) followed as the next. The long-term follow-up data from 29 months up to 150 months (mean 83.3 months) demonstrated more than 80% seizure reduction in 19 patients (27%), more than 50% seizure reduction in 18 patients (26%), less than 50% seizure reduction in 20 patients (28%), and no response in 13 patients (19%). No statistical difference in the rate of good responders of more than 50% seizure reduction was seen between patients with generalized epilepsy and localization-related epilepsy. VNS also worked for patients treated by combination of VNS and cranial surgery including failed cranial surgery. One case of complication with postoperative wound infection (1.4%) was experienced and the system was explanted immediately.

Conclusions: VNS should be considered as a treatment option when cranial surgery is not justified after sufficient discussion on the strategy for medically refractory epilepsy even in the pediatric population. VNS is especially offered to patients with generalized or multifocal epilepsy at the NYU Comprehensive Epilepsy Center. Failed cranial surgery is also one of the suitable indications. VNS works well for palliation in seizure control and is a safe treatment option for the pediatric

population even if they experience common side effects secondary to electrical stimulation.

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REPEAT SURGERY FOR MEDICALLY REFRACTORY EPILEPSY IN CHILDREN: FEATURES AND SEIZURE OUTCOME

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Rationale: Despite an initial epilepsy surgical resection, selected patients with continued medically refractory seizures may be considered for further surgery. There is little reported data on repeat operations performed in children who have not responded optimally to initial surgery. We retrospectively reviewed children who have undergone reoperation and examined their features and outcomes.

Methods: We identified patients from our epilepsy surgery database who had cortical resection for medically intractable focal epilepsy and who had a minimum of 6 months follow up from the last surgical resection. Patients who had palliative procedures (corpus callosotomy, vagus nerve stimulator), or and an initial hemispherectomy were excluded. The databases and medical records were queried for demographics, video EEG and MRI findings, seizure focus location and etiology, number and type of surgical procedures that resulted in cortical resection, and outcome (Engle classification).

Results: Twenty two of 153 patients (13%) had two or more surgical resections for epilepsy. Five of the 22 had more than 3 or more. Etiologies included: cortical dysplasia (8), tumor (6), encephalitis/ Rasmussens (3), mesial temporal sclerosis (1) and nonlesional (4). Fourteen had an initial extratemporal surgery and 8 were temporal surgeries. All had complex partial seizures (one case with focal cortical dysplasia had mixed seizures including focal seizures).

Eleven patients out of 17 (64%) with a repeat resection had a Class I Engle surgical outcome, while 3 (17%) were Class II. Only 2 (11%) had Class IV outcome. Of the five who had 3 resections, 3 (60%) had Class I outcome, 2 were Class IV (1 became seizure free when a new antiepileptic drug was started). Of those who had Class IV outcomes, 2 were nonlesional, 1 had dysplasia and 1 had dual pathology on the contralateral hemisphere with mixed seizures and multifocal spikes. All had an initial extratemporal resection.

New neurologic deficits seen after the second resection consists of 1 with homonymous hemianopsia, 5 with mild hemiparesis (2 with visual field cut and 1 with homonymous hemianopsia), and 1 with mild facial weakness. In five of these patients, they were expected deficits that led to a limited first surgery. No new deficits were seen with those with 3 resections. Only one patient had a complication developing a subgaleal hematoma postoperatively.

Conclusions: Selected patients may be candidates for further surgery if they continue to have refractory seizures. Good outcome were seen in cases were extension of the previous resection site was done and a lesionectomy was completed. An initial extratemporal resection, dual pathology and nonlesional cases were predictors of poor outcome. Minimal complication or expected neurologic deficits were seen in the second and third reoperations. Persistent re-evaluation and re-operation may be necessary to achieve seizure freedom.

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TRANSSYLVIAN SELECTIVE AMYGDALOHIPPOCAMPECTOMY IN CHILDREN: SEIZURE AND COGNITIVE OUTCOME

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Rationale: Selective amygdalohippocampectomy (SAH) is a recognised surgical treatment in adults, offering effective seizure control (seizure freedom in 70%) with good neuropsychological outcome. There are few studies in children and available data are conflicting. Comparisons are complicated by mixed pathology and differing surgical approaches and selection criteria. Small series of SAH in children with hippocampal sclerosis (HS) have shown rates of Engel I/II outcome between 56-83%. However, concerns have been raised about cognitive decline, particularly after left-sided procedures. We assessed seizure control and cognitive function after transsylvian (TS) SAH in children with suspected HS and congruent pre-operative investigations.

Methods: In a retrospective case series of children undergoing TSSAH between March 2001 and October 2008, inclusion criteria were: epilepsy resistant to medical control, age <18 yrs, HS, congruent MR imaging and EEG, and a minimum of 1 year follow up. Extratemporal resections were excluded. We assessed pre- and post-surgery the number of anti-epileptic drugs (AEDs) and neuropsychological functioning. Seizure outcome was examined according to Engel at 1 and 2 years and most recent follow-up by an independent assessor.

Results: After onset of partial seizures intractable to medical therapy at median 3.58 (range 1.5-11) years, 4 patients received right and 4 left sided TSSAH (all right-handed; 5 girls (1 left TSSAH)) at a median age of 14.2 (range 5.3-17.7) years; follow-up was 3.3 (1.0-6.8) years. All patients had a favourable seizure outcome. At most recent follow-up, all were classified as Engel I, subclassified as four Ia (50%; completely seizure free since surgery), three Ib (37.5%; auras only since surgery) and one Ic (12.5%; some seizures post surgery but seizure free >2yrs). This was improved in comparison to earlier assessment of outcome at 1 and 2 years, when all patients were Engel I or II. No patients were classified as Engel III or IV at any point during follow-up. Processing speed improved post-operatively ($p<0.05$). Full scale IQ assessment showed both improvement and decline. There were no significant changes from baseline to follow-up in general memory, learning or delayed recognition, although learning and delayed recognition were reduced in 3 of 4 fully assessed patients. Visual and verbal memory assessment similarly showed no significant changes, although one patient showed a consistent decline. There was no decline in verbal memory following left-sided resections. One patient with right-sided resection showed a paradoxical improvement in visual memory but modest decline in verbal memory. At 2 years, all patients had significantly reduced numbers of AEDs ($Z=-1.86$, $p<0.05$ one tailed).

Conclusions: In carefully selected paediatric patients, TSSAH may offer similar or improved seizure outcome comparable to adult studies. Neuropsychological results showed no consistent, substantial decline post-surgery and processing speed improved. Larger series with longer follow-up are needed to further evaluate the potential benefits of TSSAH in children.

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EPILEPSY SURGERY IN CHILDREN WITH INTRACRANIAL SHUNTS

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Rationale: Frequency of seizures in children with hydrocephalus varies from 25to 75% in the literature implicating the underlying pathology, or the treatment itself including cortical injury from shunt insertion and shunt related complications such as infection. Though some retrospective studies discuss persistence of seizures in this population, there is little mentioned on more aggressive therapies such as epilepsy surgery. We describe our patient population with both intractable epilepsy and shunted hydrocephalus who underwent epilepsy surgery

Methods: A retrospective study was performed at Rainbow Babies & Children's Hospital with IRB approval. The records of all children who underwent intracranial surgery for intractable seizures through the Rainbow Comprehensive Pediatric Epilepsy Center were reviewed from 2000 to 2009. All patients with intracranial shunts at time of epilepsy surgery were identified. Pertinent clinical data from medical charts, video-EEG reports, imaging and neuropsychological studies was collected. Follow-up was from the most recent clinic visit or other contact.

Results: Four children with intractable epilepsy and shunted hydrocephalus underwent invasive monitoring to guide resection of their seizure foci.

Demographics and etiologies of both shunts and seizures are summarized in Table 1.

All had neonatal seizures or seizures in the acute post-injury period, and subsequently developed hydrocephalus treated with shunts. Seizures recurred between 2 and 9 years of age and persisted despite multiple medications. Epilepsy surgery was performed 4 to 8 years after seizure recurrence.

All 4 patients had craniotomies on the hemisphere that contained the shunt. Three had two small craniotomies at the time of electrode insertion to avoid disturbing the shunt hardware. Two patients had undergone >10 shunt revisions prior to epilepsy surgery, both have complex shunts with 2 intracranial catheters Y'd together. One of 4 patients needed a shunt revision for the first time more than 1 year after epilepsy surgery, and subsequently had 3 more revisions. There were no shunt infections or other shunt-related complications. While 2 patients had additional resection 1 year after initial surgery, seizure freedom persists post-operatively at 5 years in 2 patients.

Conclusions: Though intracranial shunts may be associated with seizures, they were not part of the assessed epileptogenic zone in our patients.

Besides the shunt itself, this patient population has etiologies and comorbidities often predetermined as criteria for suboptimal epilepsy surgery outcomes. Though the numbers are small, our results show that successful outcomes can be achieved in children with intractable epilepsy and intracranial shunts.

Table 1

IMAGE: tables/907278_T1.jpg

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SUCCESSFUL SURGICAL TREATMENT OF INTRACTABLE EPILEPSY FOR CHILDREN WITH TUBEROUS SCLEROSIS COMPLEX

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Rationale: Tuberous Sclerosis Complex (TSC) is a dominant genetic disorder caused by mutations in either TSC1 or TSC2 genes. Brain lesions present as cortical tubers, subependymal nodules and subependymal giant cell astrocytomas (SEGA). Up to 90% of TSC patients have epilepsy, most of whom have onset in infancy or early childhood. (Jacobs J, Epilepsia 2008, 49(5):816). Epilepsy is often refractory to antiepileptic drugs (AED) and an unfavorable course has been described in those children with seizure onset in the first year of life, as their risk for developmental and social regression is compounded by their frequent seizures and epileptic encephalopathy. (Madhavan D, Epilepsia 2007, 48(8):1625). AEDs combined with non-medical treatments such as the ketogenic diet or vagal nerve stimulator (VNS) can provide adequate seizure control for a portion of these children. However, for many of them the most effective option is epilepsy surgery that sufficiently disrupts the epileptogenic network formed by multiple foci. (Weiner HL, Pediatrics 2006, 117:1494; Baumgartner J, Neurosurgery 1997, 27:311). Here we describe a stepwise surgical approach in five children with TSC and multiple epileptogenic foci that combines corpus callosotomy and cortical resection.

Methods: Five children ages 4-17 years with TSC and refractory epilepsy underwent surgery at our institution in the last three years. Age at seizure onset was between 8 weeks and 18 months of life. Seizure types were variable and included complex partial, atonic, atypical absence and mixed flexor spasms. All children experienced multiple daily seizures despite multiple AEDs and VNS (3 patients). All received a Phase I evaluation that included cerebral magnetic resonance imaging (3TMRI), video-Electroencephalogram (VEEG), and magnetoencephalography (MEG). Corpus callosotomy was performed in all patients. Phase II evaluation with bilateral subdural grids of electrodes was performed in 4 patients, and unilateral grids in one patient. Bilateral resections were performed in 4 patients, and unilateral in one. Two patients had a resection prior to care by our group.

Results: IEEG revealed multifocal but stereotypical patterns of propagation with clearly lateralized and regionalized onset. MEG spike localization was often multifocal, and coincided with IEEG patterns of seizure onset and propagation, as well as with location of tubers or areas of dysplasia seen on 3TMRI. Two patients underwent repeat phase II or III before complete seizure control was achieved, often requiring resection of multiple distinct and independent foci. All patients are currently seizure free, with period of seizure freedom ranging from 3 to 34 months. Language and social interactiveness improved in all. Surgical complications included mild hemiparesis in one patient that improved with therapy, and superficial incision infection in one patient which resolved with antibiotics.

Conclusions: A stepwise surgical approach combining corpus callosotomy and multiple resections in TSC children can lead to seizure freedom and improved developmental outcome.

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THE USE OF AN AUTOMATIC SPECT INJECTOR IMPROVES THE QUALITY OF ICTAL STUDIES IN PEDIATRIC EPILEPSY SURGERY PATIENTS

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Rationale: Single photon emission computed tomography (SPECT) has been used in the evaluation of patients for epilepsy surgery. As part of a pre-surgical evaluation, an ictal SPECT scan, which requires injection of the isotope being used (usually Tc-99m) at the onset of the seizure, can be compared with an inter-ictal study completed when the patient is not having a seizure. Electronic subtraction of the studies may reveal a region of increased cerebral blood flow identifying the seizure focus. A quality study requires an immediate injection when the seizure electrographically begins. Delayed injections may falsely localize the seizure onset. An automatic injector which could be remotely activated by a technologist monitoring the electroencephalogram (EEG) would improve the quality of the ictal study by decreasing the injection time. An automated system that does not require a nurse to directly handle the radioactive isotope and inject into a seizing patient should also improve safety and decrease spillage of the isotope. To test this hypothesis we have worked with a local company (Medrad) and adapted a commercially available injector for use with ictal SPECT studies in pediatric patients.

Methods: Medrad Corporation manufactures injectors primarily used during radiologic studies such as MRI and CT scans. We have adapted the Solaris injector, originally designed for MRI contrast injections, to be used for ictal SPECT studies. No modifications were made to the injector or the software, a lead shield was designed and added to the syringe containing the isotope. The Solaris injector was chosen due to a KVO mechanism which ensures a patent IV for the injection. If the IV line is not functional an alarm sounds and the nursing staff can correct the problem. The isotope is loaded into the syringe by nuclear medicine staff and delivered to the patient's room twice per day. The injection is activated remotely buy a technologist monitoring the EEG of the patient. When the seizure begins the EEG, the technologist presses a button on the control panel positioned next the EEG monitoring computer and the isotope is injected followed immediately by a saline flush.

Results: Since our institution began using the automatic SPECT injector, 5 patients have had successful studies. No spillage or leakage of isotope occurred. Injection times ranged from 5-20 seconds with an average of 10 seconds. Injection times have decreased as staff has become more comfortable with the injectors.

Conclusions: An automatic SPECT injector can be easily made by adapting the Medrad Solaris MRI injector without any software or hardware changes required. By adding fiber-optic cable to our patient rooms and working with our radiation safety personal to develop a custom lead shield we have been able to use the injector without difficulty. With the injector we have had no spillage of isotope and our injection times have decreased to an average of 10 seconds improving the quality of the studies. Improved quality of ictal SPECT studies allows more patients to have successful epilepsy surgery.

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THE EFFECT OF VNS THERAPY ON BODY MASS INDEX IN CHILDREN

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Rationale: In animal studies, vagotomy leads to diminished satiety, while stimulation of the vagus nerve has the opposite effect with consequent decreased weight in canine and rat models. Therefore, the vagus nerve is thought to play a role in mediating hunger. The effects of vagus nerve stimulation (VNS) on weight in individuals being treated for epilepsy have yet to be fully characterized. Prior studies have examined changes in weight for patients with VNS as opposed to the more informative measure of body mass index (BMI) percentile.

Methods: We performed an IRB-approved, retrospective, observational, cohort study on pediatric patients that underwent VNS placement at Duke University Medical Center from 2001 to 2009. The following were obtained prior to surgery and at follow-up visits: age, gender, weight, height, and seizure type. In addition, the number of anti-epileptic drugs (AEDs) which reduce and increase weight were recorded at baseline and last follow-up appointment. Baseline BMI percentile was compared to percentile on follow-up visits using a paired sample t-test. Bivariate analysis was performed to find variables that were significantly associated with change in BMI percentile at follow-up.

Results: We studied 23 patients who had undergone VNS placement. Baseline BMI percentile was 61.7 ± 34.3 (n=23). At one year follow-up (mean 345 ± 112 days), and last follow-up (mean 4.2 ± 2.4 years) the average BMI percentile was 61.6 ± 31.88 (n=20) and 56.09 ± 30.83 (n=23), respectively. There was no significant difference in BMI percentile as compared to baseline at 1 year and at last follow-up visit (p= 0.992 and 0.681, respectively). On bivariate analysis, change in BMI percentile was negatively correlated with the BMI at baseline (p=0.035), but had no correlation with age, gender, number of days to last follow-up visit, number of AEDs which reduce weight at baseline and follow-up, number of AEDs that increase weight at baseline and follow-up, and seizure type (pe"0.058 for all).

Conclusions: Long term pediatric VNS therapy does not have clinically significant effects on BMI percentile during follow-up for up to an average of over four years.

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OUTCOME AND COMPLICATION IN HEMISPHERECTOMIES OF INFANTS LESS THAN A YEAR OLD

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Rationale: Only 2 studies document the efficacy and complication of hemispherectomies in infants.

Methods: This is a chart review of 11 infants with hemispherectomies from 2003 to 2010 (7 boys, 4 girls). All had presurgical evaluation including brain MRI and EEG monitoring. Preoperative data included

development, age at surgery and seizure onset, seizure type, treatments tried prior to surgery, EEG, MRI and functional neuroimaging results. Perioperative data included blood loss during surgery and hospital length of stay. Postoperative data included surgical complications, pathology, and seizure frequency after 6 months, 1 year, 2 years and 4 years.

Results: Seizures started on the first day of life for 2, in the first 2 weeks of life for 6, and within the first 6 months for 3. Five children had complex partial seizures (CPS), 2 had infantile spasms (IS) and 4 had both; all had EEG with onset from one hemisphere. Ten infants tried at least 2 medications prior to surgery except one with hemimegalencephaly and status epilepticus severe enough to warrant surgery at 2 weeks old. One patient had a trial of the ketogenic diet. On MRI, there were 4 with cortical dysplasia (CD), 1 with Sturge Weber, 2 with hemimegalencephaly (1 also with linear nevus syndrome), 1 with encephalomalacia from hemorrhage and 1 with a normal MRI. In this patient, a follow-up MRI showed hyperintensity in the basal ganglia and cerebellum consistent with vigabatrin toxicity and an electrocorticography demonstrated spikes over the entire hemisphere. Four had interictal PET scans with 3 showing hypometabolism on the affected side; one had an ictal PET with hypermetabolism over the affected side and in the peri-insular cortex on the opposite hemisphere.

All patients had a functional hemispherectomy (5=right, 6=left). One patient had a 2 stage hemispherectomy performed first at 1 week of age then completed at 2 weeks of age due to autonomic instability. Age at surgery ranged from 14 days to 12 months of age. Hospital length of stay, estimated blood loss and fluid resuscitation were similar compared to older patients.

Pathology revealed 9 with CD, one with gliosis and one with findings consistent with Sturge Weber. Follow-up ranged from 2 months to 5 years (mean 21.9 months). Six patients were seizure free, 3 with isolated seizures within the first 2 months of surgery and 1 with a 90% improvement in seizures. One had 50% improvement in seizures. Four had normal language development. No mortality occurred. All patients had hemiparesis and visual field cut. Four patients required a ventriculoperitoneal shunt (VPS) due to increased intracranial pressure. One had growth failure later.

Conclusions: 1)No significant morbidity or mortality was noted. 36% required VPS.

2)Seizure freedom occurred in 55% with the rest benefiting significantly from surgery.

3)81% had CD. This may represent the importance of malformations as a primary etiology in this young population.

4)55% had IS demonstrating a predisposition for this catastrophic seizure type in this population. Further studies are needed to confirm these findings.

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CLINICAL OUTCOMES IN REOPERATION AFTER COMPHREHENSIVE EPILEPSY SURGERY

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Rationale: To determine predictive factors of clinical outcome following reoperation after comprehensive epilepsy surgery.

Methods: The authors retrospectively studied the operative outcome in 19 consecutive patients who underwent reoperation for intractable epilepsy. We monitored the patients at least 1 year after reoperation. Epidemiologic data and preoperative electrographic and radiologic findings were examined.

Results: Average age of seizure onset was 2.01±2.51 year. The average duration between seizure onset and first operation was 2.68±3.39 year.

The mean duration between the primary operation and second operation was 1.98±2.24 year. Twelve patients(63.15%) had cortical dysplasia , three had Rasmussen encephalitis, Cerebromalacia, Hippocampal sclerosis and the other four had unknown etiology. Among fourteen patients with cortical dysplasia, six had mild malformation of cortical dysplasia and eight had focal cortical dysplasia.

The primary operation were resective surgery (n=13, 68.42%)and hemispherotomy(n=6, 31.57%). Four patients (21.05%) underwent three times of operations. Sixteen patients underwent reoperation due to incomplete resection (84.21%) and three due to late recurrence (15.78%). The outcome was Engel class 1, 2 in thirteen patients(68.42%)and Engel class 3, 4 in six patients (31.57%). Statistically significant factors related to reoperation outcome were sustained electrographic abnormalities in postoperative EEG and concordance between SISCOM and other tools including Brain MRI, FDG-PET and video EEG monitoring($P<0.005$). Twelve patients(63.15%) had subdural hemorrhage as postoperative complication and eleven (57.89%) had permanent neurologic deficits.

Conclusions: Reoperation may be an alternative treatment option for patients with intractable epilepsy who failed to control seizure after initial operation.

2.292

BILATERAL MULTISTAGE APPROACH IN EPILEPSY SURGERY

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Rationale: To evaluate the utility of a bilateral multistage approach with intracranial EEG using subdural electrodes in epilepsy surgery.

Methods: We reviewed the records of 11 patients (M 8/F 3, mean age 11.3 years, range 6 months-21 years) with medically intractable epilepsy who underwent bilateral invasive EEG monitoring at Cincinnati Children's Hospital Medical Center between October 2006 and November 2009. Clinical characteristics, presurgical evaluation, intracranial EEG findings, type of surgery, and surgical outcome were observed.

Results: The reason for bilateral multistage approach included unlocalizing ictal onset on scalp EEG (5/11, 45%), bilateral independent ictal onset on scalp EEG (4/11, 36%), discordance between MRI abnormality and ictal onset on scalp EEG (1/11, 9%) and bilateral MRI abnormality (1/11, 9%). In six (55%) patients, subdural grid was placed in one selected hemisphere for the second stage, based on ictal EEG findings during bilateral monitoring as the first stage. Ten (91%) patients underwent resective surgery following bilateral invasive EEG monitoring, and five (50%) out of 10 achieved seizure-freedom at least 6 month follow-up. In one patient, subdural electrodes were removed without resective surgery since ictal EEG showed bilateral synchronous

onset in both hemispheres. No patient experienced major complication due to subdural electrodes placement.

Conclusions: Our results suggest that multistage approach using bilateral subdural electrodes is safe and effective in a challenging and selected epilepsy patient group.

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HYPONATREMIA IN PEDIATRIC PATIENTS UNDERGOING INTRACRANIAL MONITORING AND EPILEPSY SURGERY FOR INTRACTABLE PARTIAL SEIZURES

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Rationale: Hyponatremia is a known complication of intracranial surgery. The goal of this study was to describe risk factors for hyponatremia in pediatric patients undergoing intracranial monitoring (phase II) and epilepsy surgery (phase III) for partial seizures.

Methods: The charts of pediatric epilepsy patients who underwent intracranial monitoring followed by epilepsy surgery for intractable partial seizures were analyzed. Patients who developed hyponatremia in the peri-operative period were identified, and their records were reviewed.

Results: Of 61 pediatric patients who underwent intracranial monitoring and epilepsy surgery (phases II and III) for partial seizures in a 4.5 year period, 33 (54%) patients developed hyponatremia (Na d" 134) during the hospitalization despite normal sodium at admission. In 9 (27%) of these patients the lowest sodium measured was 134. However, 10 patients (30%) had a sodium nadir less than or equal to 130. Of these 10 patients, seven (70%) were on oxcarbazepine. Eight (80%) of the 10 patients had surgery involving the left hemisphere, and nine (90%) had resection of the temporal and/or occipital lobes. Sodium replacement was performed in 3 patients (ages 7-18); two of the patients had severe hyponatremia (sodium <125), and the third's lowest value was 128. The patient with the lowest nadir (120) had a history of glioma status past resection and radiation, meningococcal meningitis, and hypopituitarism. All 3 of the patients who underwent sodium replacement experienced hyponatremia with both phases II and III, with lower sodium values following resection. One patient underwent left temporal lobectomy, one underwent a left occipital resection, and one underwent a left temporal-occipital resection. All three patients were taking oxcarbazepine in addition to a second anti-epileptic drug (zonisamide or levetiracetam). The patient whose sodium nadir was 128 was maintained on oxcarbazepine, and the other two were changed to another anti-epileptic medication. One of these patients resumed oxcarbazepine following discharge.

Conclusions: Hyponatremia is common in the setting of intracranial electrode placement and epilepsy surgery, occurring in more than half of the patients. Most of the time, it resolves without intervention. This study suggests that oxcarbazepine may be a risk factor for hyponatremia in the peri-operative period. Also, resection of the left temporal and/or occipital lobe(s) appeared to be a risk factor. Further studies are needed to clarify the role of oxcarbazepine and whether the hemisphere or lobe of resection affect risk.

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REPEAT SURGERY OF HYPOTHALAMIC HAMARTOMA FOR REFRACTORY EPILEPSY

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Rationale: Hypothalamic hamartomas (HH) often cause pharmacoresistent epilepsy, incapacitating behavioral abnormalities, and cognitive decline. Surgical intervention offers the patient the best opportunity for eradication of intractable epilepsy (up to 50% of patient achieve seizure free) and improvement in cognitive function and behavioral problems. For those who failed the first surgery, further treatment options are quite limited, and at times, second surgery may improve seizure outcome. We reviewed our surgery patients to document the success and complications of reoperation after failed first surgery.

Methods: Data was obtained from our Hypothalamic hamartoma epilepsy surgery database at the Barrow Neurological Institute between 2003 and 2010. Surgical treatment consisted of open and endoscopic procedures, as well as radiosurgery and interstitial radiotherapy. Demographic details, seizure history, presurgical evaluation, and postoperative follow up data were evaluated.

Results: In the last seven years 21 out of 157 patients (13%) underwent reoperation after failed first epilepsy surgery. Initial surgical approach of the 21 patients included: endoscopic (N=8; 38%), transcallosal (N=7; 33%), orbitozygomatic (N= 3; 14%) , radiosurgery (N =2; 9 %), and transpshenoidal (N=1; 4%). Of the 8 patients with failed endoscopic resection repeat procedures were: radiosurgery (N=4; 50%), orbiotozygomatic (N=2; 25%), repeat endoscopy (N=1) and transcallosal approach (N = 1). Reoperation for the failed transcallosal resection patients included: endoscopic (N=2); radiosurgery (N=1); orbitozygomatic (N=2) and repeat transcallosal resection (N=2). Predominant seizure types that recurred after failed surgery were: gelastic seizures, complex partial and tonic-clonic type. MRI brain in all patients prior to reoperation demonstrated residual HH. Review of patients with more than six months follow-up (vast majority) since the second operation showed that greater than 50% of patients had a >50% seizure reduction although none were seizure free. Following reoperation, none of the patients had any worsened behavioral issues like increased rage attacks, disruptive violent behavior. New postoperative complications after reoperation included: hemiparesis, thalamic stroke (asymptomatic and symptomatic), hyperphagia and panhypopituitarism.

Conclusions: Reoperation should be considered in selected HH patients failing epilepsy surgery because more than half the patients have significant seizure reduction.

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EARLY SURGERY FOR INFANTILE INTRACTABLE EPILEPSY ASSOCIATED WITH HEMIMEGALENCEPHALY

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Rationale: Hemimegalencephaly (HME) is a severe malformative condition and usually patients exhibit catastrophic epilepsy that

develops soon after birth. We describe seizure control and developmental outcome following vertical parasagittal hemispherotomy(VPH) for infantile intractable epilepsy with HME.

Methods: Retrospective analysis of 12 patients (ages 2 -9 months) who underwent VPH from 2003 to 2009 with a minimum follow-up period of 1 year.

Results: 11 patients (92%) exhibited preoperatively early epileptic encephalopathy with suppression-bursts. Mean preoperative developmental quotient (DQ) was 33.5. Mean age at surgery was 4.5 months. After VPH, 8 patients (67%) were Engel Class I and 4 continued to have seizures and were classified as Engel Class II(1 case) III (1 case) or IV (2 cases) . Patients with favorable seizure outcome(Class I+II) showed an increase in DQ.

Conclusions: Early VPH should be considered for infantile intractable epilepsy with HME, despite severe diffuse electroencephalogram abnormalities.

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QUALITY OF LIFE CHANGES FOLLOWING PEDIATRIC EPILEPSY SURGERY

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Rationale: While quality of life (QOL) has been accepted as a primary outcome variable in pediatric epilepsy, there remains limited information about how different treatments affect or enhance QOL (Choi, et al., 2008). Zupanc, et al. (2010) recently published a comprehensive study on QOL outcomes from epilepsy surgery (N = 52); however, their study was limited by the lack of presurgical QOL information for comparison. Therefore, they were unable to comment on changes since the surgery and were limited to describing post-surgical QOL. The present investigation was designed to examine actual changes in QOL in children who undergo epilepsy surgery by comparing parent ratings of QOL before surgery and after surgery.

Methods: Twenty eight children who underwent epilepsy surgery at St. Louis Children's Hospital between 2006 and 2009 were selected for this investigation because of the availability of both pre- and post-surgical neuropsychological data. The study was approved by the institutional review board, and the data were compiled through archival investigation. Pre- and post-surgical QOL data consisted of parent ratings on the Quality of Life in Childhood Epilepsy (QOLCE) questionnaire (Sabaz et al, 2003). Cognitive changes following surgery were considered by comparing scores on the Wechsler Abbreviated Scale of Intelligence. Pre- and post-surgical changes were analyzed with paired t-tests or Wilcoxon's signed rank test.

Results: The mean age of the sample at the time of surgery was 12.7 years (SD=2.6), and they were Caucasian and mostly male (54%). Mean post-surgical follow-up time was one year. While the children in the sample demonstrated stable full scale intelligence following surgery (p=0.74), parent reports on the QOLCE revealed significant improvements in Total QOL (p=0.002), as measured by calculating a mean of the subscale scores. When asked more subjectively, parents confirmed significant improvements in QOL (p=0.01), and they rated their children as having significant improvements in general health ($p<0.0001$). On individual subscales, parents rated significant improvements in most aspects of QOL, including behavior (p=0.004), physical activities (p=0.01), and social activities (p=0.004). However, changes in QOL related to cognition (p=0.06) and general well-being (p=0.11) were below statistical significance.

Conclusions: These results reveal evidence of significant improvements in the QOL of children following epilepsy surgery. This improvement is apparent despite the fact that the children, as a whole, displayed no changes in intellectual functioning and limited improvements in cognitive functions related to QOL (e.g., making decisions). Nevertheless, improvements in QOL are evident in most other areas, including behavioral, physical, and social functioning. Interestingly, QOL related to well-being, which assesses emotional functioning and self-esteem, did not change significantly after surgery. This may indicate an important clinical feature of this population that may need to be monitored by caregivers, even in the presence of stable to improved functioning in other areas.

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PRESURGICAL INVASIVE EXPLORATIONS IN CHILDHOOD EPILEPSY: OUR EXPERIENCE WITH SUBDURAL ELECTRODES AND STEREO-ELECTROENCEPHALOGRAPHY

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Rationale: Despite remarkable advances in the presurgical evaluation of drug-resistant focal epilepsy, intracranial EEG remains essential in several cases. The choice between subdural or depth recording depends on the experience and preference of each epilepsy surgery team. As for now, there exists no guidelines for which technique should be used in a given case.

Methods: At our institution, we use both techniques, subdural grid recording and stereo-electroencephalography (S-EEG) in children. For each patient, all noninvasive data are extensively discussed and the type of recording is individually planned.

We reviewed the charts of the 252 invasive explorations in children aged from 3 months to 15 years, performed between 1995 and 2009. We tried to define clear-cut rules concerning the choice of each method.

Results: Subdural electrodes had been placed in 92 children through open craniotomy, with a few additional depth electrodes, positioned with the guidance of intraoperative echography or MRI-based neuronavigation, in order to better explore cortical regions in the depth of a sulcus and the insular cortex when indicated. Complications were meningitis in three, bone infections in two, and subdural hematoma in four children. In the same period, 160 children underwent robot-assisted, stereotactic placement of multiple depth electrodes (6 to 15 electrodes per procedure) for S-EEG, with the occurence of epidural hematoma in two children. There was no postoperative neurological deficit.

In children younger than 2.5 years of age, electrodes were exclusively placed through craniotomy, since a minimum skull thickness is required for stereotactically implanted multiple depth electrodes. Only two of the 92 children (2%) who had been explored with subdural electrodes were excluded from resective surgery, whether this was the case in 20% of the children following S-EEG.

In older children, S-EEG was the predominant recording technique. However, we prefered subdural grids when exploration of eloquent cortex required functional mapping. In children with very extensive malformations, there are limitations in craniotomy size for complete subdural covering, whereas with S-EEG, it is difficult to insert a sufficient number of electrodes to properly delineate the lesion.

Conclusions: Subdural recording is the unique method to be used in infants and provides a better means for delineating the border of a known lesion over the convexity or when functional cortical mapping is required. S-EEG is preferable when the location of the epileptogenic zone is only hypothetical or when the study of a long-distance propagation is mandatory. The two invasive approaches should not be considered as opposites but can rather be complementary ways for an optimal presurgical assessment in complex focal epilepsies. The future challenges are to perform S-EEG in infant surgical candidates and to better combine both techniques.

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COMPLETE SECTION OF THE CORPUS CALLOSUM ASSOCIATED WITH VAGAL NERVE STIMULATION FOR ATONIC SEIZURES IN PEDIATRICS

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Rationale: Corpus callosum section is an effective procedure for atonic seizures with bilateral synchrony associated with head drops. Vagal nerve stimulation (VNS) has been used for refractory seizures; the usefulness of both procedures in head drops has been of increased interest.

Methods: Patientes with complete corpus callosotomy and VNS were evaluated.

Results: 4 patients with refractory seizures were included; the mean age at surgery was 5 years. All patients had head drops but not exclusively, the mean follow-up was at least 3 years. In all the patients there was a reduction in the number of seizures higher than 80 %. None of the cases were seizure free after the procedures, although significant seizure reduction was accomplished after the first operation. The interval of seizure reduction was greater with the combination of both interventions than with either procedure alone.

Conclusions: Complete corpus callosotomy is more affective associated vagal nerve stimulation, the seizure reduction is greater and the functionality of patients is improved even in the cases with associated heterogeneous seizure presentations.

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REACTIVATION OF HERPES SIMPLEX VIRUS ENCEPHALITIS FOLLOWING EPILEPSY SURGERY

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Rationale: Relapse of Herpes Simplex Virus (HSV) encephalitis following successful antiviral therapy is uncommon but well described. It is more frequent in children and usually occurs within 3 months of initial infection. Later relapse is rare. A case of reactivation of HSV encephalitis triggered by epilepsy surgery 16 years after initial infection is reported, and similarities to a single previous case report are reviewed.

Methods: A case of recurrent HSV encephalitis following right frontal topectomy for intractable epilepsy is presented, with comparison to a prior report (Bourgeois M et al, Reactivation of herpes virus after surgery for epilepsy in a pediatric patient with mesial temporal sclerosis. Neurosurgery, 1999; 44(3):632-635.)

Results: A 19 year old woman with prior HSV encephalitis at age 3 years developed refractory frontal lobe epilepsy (10-20 seizures/day). After 7 days of invasive monitoring with subdural electrodes, right inferior frontal gyrus topectomy and MST of surrounding area was performed. She was seizure-free until postoperative day (POD) 10 when she presented with fever, headache and CSF WBC=125(68% PMN). MRI showed acute right frontoparietal infarction and small areas of restricted diffusion in left hemisphere. Mental status worsened with persistent fever despite IV vancomycin, ceftriaxone and open irrigation of surgical site. On POD 19 fever had resolved but MRI showed new areas of bilateral infarction, CSF WBC=10 (83% Lymph) and CSF PCR positive for HSV. Despite initiation of acyclovir there was extension of intracranial edema and patient expired on POD 25. Postmortem confirmed HSV encephalitis with positive virus immunostaining.

Comparison is made to a single previous case report of HSV encephalitis at age 16 months with reactivation following amygdalohippocampectomy at age 8 years. That case presented similarly on POD 6 with fever, deterioration in neurological status and diffuse cerebral involvement, maximal at surgical site. Patient survived with severe disability. Notable differences were the shorter interval between original infection and recurrence (7 years vs. 16 years), lack of invasive subdural monitoring, and status epilepticus at presentation.

Conclusions: Epilepsy surgery may induce reactivation of HSV encephalitis in previously affected patients. The use of subdural electrodes, corticosteroids and surgical manipulation may have acted as triggers for reactivation in the current case. Diagnosis was complicated by the preceding invasive monitoring, which increased suspicion for bacterial infection, and by neuroimaging which suggested infarction rather than encephalitis. Length of time between original encephalitis and surgery does not appear to mitigate the risk for reactivation, as our case represents the longest reported interval between initial infection and reactivation. The poor outcome of these patients underscores the need for a high index of suspicion for herpes reactivation and early use of acyclovir in at risk postoperative patients. Prophylactic acyclovir should be considered in patients with a history of encephalitis undergoing invasive monitoring.

2.300

COMPARISON OF OUTCOME AFTER CALLOSOTOMY AND VAGUS NERVE STIMULATION THERAPY IN CHILDREN WITH DROP ATTACKS

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Rationale: Children and young people with refractory seizures have a significant morbidity and disability. Corpus callosotomy and vagus nerve stimulation (VNS) therapy are two commonly used palliative

epilepsy surgeries for children with medical resistant epilepsy not amenable to curative resective surgical procedures. The aim of this study was to compare the efficacy of corpus callosotomy and vagus nerve stimulation (VNS) for the treatment of drop attacks.

Methods: Retrospective case notes review of children and young people with drop attacks as mainly and more disabling type of seizures underwent corpus callosotomy or vagus nerve stimulation (VNS) at Great Ormond Street Hospital between 1993 and 2009. Our Service has been implanting VNS since 2005.

Results: Corpus callosotomy: from 1993 to 2004, six patients (83% male), with a mean age seizure onset 3.6±3.3 years and surgery 12±5 years. 2/ 6 had a normal brain MRI. At the last follow up, only one patient was drop attack free but was not seizure free. Following surgery, one child developed a mild monoparesis which rapidly improved. One child underwent completion of callosotomy, and two have been offered VNS implantation.

Since 2005, twelve patients (75% male), with a mean age at seizure onset of 1.6±2 years and at surgery of 11±5 years, have been identified. 7/ 12 had a normal MRI. One of them had a previous right temporal lobectomy and two had previous VNS implant. At the last follow up, one patient was drop attack free but was not seizure free. Following surgery, one child showed some degree of in-coordination, another child had left-sided weakness; both improved over time. One had difficulty in initiating speech. Two children underwent completion of callosotomy and further 4 have been evaluated for VNS implantation.

VNS: seven patients (29% male), with mean age seizure onset 3.6±3.4 years and surgery 10 ±5.1 years. 4/ 7 had a normal brain MRI. No child was drop attack and seizure free at last follow up. In one child the device was switched off for inefficacy and two children have been evaluated for callosotomy.

Conclusions: This preliminary study both corpus callosotomy and VNS reduce seizure frequency in children with intractable epilepsy not candidates for curative resective surgical procedures, but have an equal chance of effect on drop attacks. They were both safe with a low incidence of complications after surgery.

2.301

VALUE OF COMPUTED TOMOGRAPHY (CT) SCAN IN CHILDREN WITH MEDICALLY REFRACTORY EPILEPSY CAUSED BY FOCAL CORTICAL DYSPLASIA

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Rationale: This study is to examine the value of CT scan in children with medically refractory epilepsy (MRE) caused by focal cortical dysplasia (FCD) with regard to seizure outcome and types of FCD.

Methods: Seven patients with MRE caused by FCD and focal hyperintensity in CT scans who were consecutively treated with focal resection of epileptogenic region (ER) between 2004 and 2008 were reviewed retrospectively. All patients had extraoperative intracranial EEG monitoring prior to surgery. The patients with hemimegalencephaly and tuberous sclerosis were excluded.

Results: Age at seizure onset ranged from 1 day to 53 months (median 7 months, mean 14 months). Two patients had seizures in utero (excessive fetal movement and hiccup). Four patients had prenatal risks including viral infection in 1, congestive heart failure in 1, and prematurity (24 and 28 weeks GA) in 2. All patients had pathologic handedness, left in 4 and right in 1 patient. All had developmental delay (DD) with 4 patients had mildly and 3 had moderately DD. Locations of FCD were multilobar in one, frontal in two, fronto-parietal in two, parietal in one and lateral temporal in one patient. All patients had abnormal MRIs which were concordant with the CT scans. Five patients had focal transmantle dysplasia. SPECT and PET scans were done in 4 patients and all were concordant with the CT scans. Interictal EEG showed focal epileptiform activity in 5 and regional epileptiform activity in 2 patients. Ictal EEG showed focal onset in 4, regional onset in 1, and lateralized onset in 2 patients. Age at surgery varied from 1 to 138 months (median 31 months, mean 55 months). All patients had complete resection of ER. Five had mild hemiparesis and 2 had no neurologic deficit. Pathology showed severe FCD in all with FCD 2A in 2 and 2B (balloon cell-typed) in 5 patients. Pathology showed calcifications in 6 patients. All patients have been seizure free. Follow up ranged from 23 months to 6 years (median 53 months; mean 49 months).

Conclusions: Focal hyperintensity in the CT scans of patients with MRE caused by FCD is valuable in presurgical evaluation and associated with the followings; 1) severe FCD type, most commonly balloon cell-typed FCD with calcification; 2) abnormal MRI scan especially with focal transmantle dysplasia in extratemporal region; 3) high prenatal risks; 4) focal abnormalities in the EEG; 5) excellent seizure outcome after the surgery; 6) low risk of surgical complications despite the location in eloquent cortex, probably due to plasticity; 7) high risk of DD despite successful epilepsy surgery. The major limitations of this study are retrospective design, small numbers of patients, and selective bias because CT scan is not a routine evaluation tool for epilepsy surgery.

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DRUG WITHDRAWAL IN THE EPILEPSY MONITORING UNIT: OUTCOMES IN A NEWLY ESTABLISHED SERVICE

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Rationale: Drug withdrawal is often necessary in the Epilepsy Monitoring Unit (EMU) to facilitate seizures, and particularly used for children undergoing pre-surgical evaluation. There is an increasing emphasis worldwide on EMU safety, however literature detailing outcomes of drug withdrawal is sparse. In units with limited resources (including access to ictal SPECT) strategies for drug withdrawal need to be tailored to accommodate patient safety and the individual unit resources. This is a review of data from a newly established service.

Methods: Retrospective review of EMU and hospital record data of patients with intractable epilepsy admitted for pre-surgical Video-EEG evaluation (+/- ictal SPECT) and undergoing drug withdrawal at the Royal Children's Hospital EMU, Brisbane. This EMU currently has limited access to ictal SPECT services (4-6 morning sessions per month, each with a 3 hour window, and a maximum of two consecutive sessions per week). During periods of drug withdrawal patients have a carer present at all times, intravenous access and continuous overnight oximetry, and an individualized management plan for prolonged seizures. Patients are reviewed 1-2 times daily by a Paediatric Epileptologist/Epilepsy fellow, and EEG scientists monitor patients during normal working hours. Patient data reviewed included seizure history, seizure frequency during admission, status epilepticus (SE), the inpatient drug withdrawal strategy, success of admission (i.e. typical seizure achieved, +/- SPECT when relevant), and need for emergency management.

Results: There were 31 admissions (28 patients) from May 2008 to May 2010. Pre-admission seizure frequency was less than weekly in 7 patients; 12 patients had a history of SE. Drug withdrawal was individualized, based on the patient seizure history and anticonvulsant medication type. Drug withdrawal was full (3 admissions) or partial (28 admissions) and commenced on the first day in 17 admissions. Three patients had partial withdrawal of chronic benzodiazepine treatment. The admission was successful in 25 patients (typical seizures obtained); of these, ictal SPECT imaging was achieved in 17. SPECT imaging was not able to be achieved during 3 admissions due to lack of seizures occurring in the allotted time, including 1 patient with an unsuccessful attempt on repeat admission. Overall seizure frequency increased during 15 admissions, decreased in 4 admissions, and remained unchanged in 12. Benzodiazepine treatment was required for prolonged seizures on 6 occasions, including 2 episodes of SE. There were no admissions to the intensive care unit.

Conclusions: Tailored drug withdrawal can achieve successful results in the EMU, even in the presence of limited resources. There is a requirement for individualized patient management to provide the safest possible outcomes.

2.303

HIPPOCAMPAL DEEP BRAIN STIMULATION (HIP-DBS) IN PATIENTS WITH BILATERAL TEMPORAL LOBE EPILEPSY (TLE) AND NORMAL MRI FINDINGS OR BILATERAL MESIAL TEMPORAL SCLEROSIS (MTS)

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Rationale: Patients with TLE represent the most suitable candidates for epilepsy surgery. On the other hand, patients with TLE and normal MRI findings or with bilateral MTS represent a challenge for surgical treatment. Patients with normal MRI and dominant TLE are at high risk for cognitive decline after cortico-amygdalo-hippocampectomy. We present our experience Hip-DBS, a non-resective technique, in this patient population.

Methods: Six patients with bilateral interictal temporal lobe spiking and non-lateralized ictal video-EEG recordings were studied. Three had normal MRI and 3 had bilateral MTS. All patients were submitted to pre- and post-operative standard neuropsychological testing. All patients were implanted bilaterally in the hippocampus using a Kinetra device. The electrodes were inserted along the axis of the hippocampus through a posterior approach; the most anterior contact was positioned in the head of the hippocampus. Pre-, intra- and post-stimulation scalp EEG recordings were obtained in all patients intra-operatively. Continuous stimulation was carried out using 300usec, 130Hz, 4-6V pulses.

Results: In 4 patients, an increase in temporal lobe spiking was noticed unilaterally at the time of electrode insertion; no bilateral increase was noted. In all patients an ipsolateral temporal lobe recruiting response was noted during acute stimulation. In 5 patients, high frequency intraoperative hippocampal stimulation reduced or abolished interictal spiking. Four patients (2 with normal MRI; 2 with bilateral MTS) received unilateral and 2 bilateral stimulation (1 with normal MRI and 1 with bilateral MTS) so far. Two patients with unilateral stimulation are seizure free and the other two had at least 90% reduction in seizure frequency. One patient with bilateral hippocampal stimulation had 70% reduction and the other one got 80% reduction in seizure frequency. There was no memory decline in patients submitted to bilateral hippocampal stimulation. Mean follow-up time was 9 months.

Conclusions: Hippocampal stimulation seems to be a very effective and safe non-resective technique in this patient population. Memory decline did not occur with bilateral hippocampal stimulation suggesting that Hip-DBS did not lead to complete inactivation of the mesial temporal lobe structures.

2.304

CENTRO-MEDIAN DEEP BRAIN STIMULATION (CM-DBS) IN PATIENTS WITH REFRACTORY SECONDARY GENERALIZED EPILEPSY PREVIOUSLY SUBMITTED TO CALLOSAL SECTION

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Rationale: Vagus nerve stimulation and callosal section are the available palliative surgical options in patients with secondary generalized epilepsy. DBS has been increasingly used in the treatment of refractory epilepsy over the last decade. We report on the outcome after CM-DBS in patients with generalized epilepsy who had been previously treated with extended callosal section.

Methods: Six consecutive patients with generalized epilepsy who were previously submitted to callosal section and had at least 1 year of follow-up after deep brain implantation were studied. Age ranged from 10 to 44 years. All patients were submitted to bilateral CM thalamic DBS. Post-operative CT scans documented the electrode position in all patients. All patients had pre- and post-stimulation prolonged interictal scalp EEG recordings, including spike counts. Attention level was evaluated by means of the SNAP-IV questionnaire. The pre-implantation anti-epileptic drug regimen was maintained post-operatively in all patients. Continuous stimulation was carried out using 300usec, 130Hz, 4-6V pulses.

Results: Post-operative CT documented that all electrodes were correctly located. There was no morbidity or mortality. Seizure frequency reduction ranging from 55 to 95% and increased attention level was seen in all patients. Interictal spiking frequency was reduced from 25 to 95%, but their morphology remained the same. There was re-synchronization of interictal discharges during slow-wave sleep in 3 patients.

Conclusions: All patients benefit from the procedure. The CM seems to play a role in modulating the epileptic discharges and attention in these patients. On the other hand, it is not the generator of the epileptic abnormality and appeared not to be involved in non-REM sleep-related interictal spiking modulation.

2.305

DIFFERENCES IN SEIZURE FREQUENCY DURING SCALP VERSUS INTRACRANIAL VIDEO/EEG MONITORING

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Rationale: A common impression among clinicians is that patients undergoing workup for epilepsy surgery have fewer seizures during intracranial video/EEG monitoring than during scalp video/EEG monitoring. The possible transient decrease in seizures may be an immediate effect of anesthesia, pain medication, or the implant surgery. The objective of this study was to examine the changes in seizure frequency during scalp and intracranial video/EEG monitoring and to identify reasons for the differences.

Methods: Retrospective review of 193 patients with intractable epilepsy with both inpatient scalp video/EEG monitoring and intracranial video/EEG monitoring in a comprehensive epilepsy program between 1992 and 2009. Number of seizures per day during each monitoring period, number of days to first seizure, AED, pain medications, types of implanted electrodes, and anesthesia agents were reviewed. Linear regression and t-test were performed for statistical analysis.

Results: During scalp video/EEG monitoring, patients experienced an average of 1.38 ± 0.85 seizures/day and an average of 1.467 ± 0.123 seizures/day during intracranial monitoring ($p>0.05$). Patients were off all AED for a mean of 1.27 ± 0.152 days during scalp and 3.00 ± 0.312 days during intracranial monitoring ($p<0.0001$). Patients experienced their first seizure after an average of 1.78 ± 0.104 days during scalp and after 2.30 ± 0.227 days during intracranial monitoring. The number of days to first seizure was significantly longer during intracranial monitoring ($p=0.018$). Fifty patients (25.9%) had no seizures until the fourth day or later of intracranial monitoring. Four patients had no seizures during their entire admission for intracranial monitoring, despite extending the monitoring period up to 21 days in one patient. 118/193 (61.1%) of patients received grid implants, while the remaining patients received a combination of depth and strip electrodes. Patients with grids experienced a significantly greater decrease in mean seizure frequency as compared to patients with depth and strip electrodes ($p=0.005$). Patients received a mean of 33.4 milligrams of morphine equivalents during intracranial monitoring. Seizure frequency during intracranial monitoring was inversely related to total morphine equivalents received. Location or pathology did not influence the occurrence of first seizure or change in seizure frequency during intracranial monitoring ($p>0.05$).

Conclusions: Seizures take longer to record during intracranial monitoring as compared to scalp monitoring. A quarter of the patients require monitoring for >4 days. AED withdrawal can be pursued aggressively during intracranial monitoring. The type of intracranial EEG implant and number of morphine equivalents have a significant impact on seizure frequency.

2.306

CAN ACUTE ELECTROCORTICOGRAPHY OBVIATE THE NEED FOR CHRONIC IMPLANTATION OF ELECTRODES AND PREDICT OUTCOME IN A SUBGROUP OF PATIENTS WITH TEMPORAL LOBE EPILEPSY AND A NORMAL MRI?

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Rationale: Patients with temporal lobe epilepsy (TLE) and normal MRI scans present a challenge to surgical therapy because neocortical and mesial TLE can be indistinguishable. In these patients, chronic implantation of intracranial electrodes is often employed to guide temporal lobe resection. Such a two-stage surgery carries increased morbidity, length of stay and cost compared with a standardized anteromedial resection (SAMR). Recent studies indicate that interictal spikes may be useful in localizing ictal onsets in TLE. We hypothesized that we could use acute intraoperative ECoG to identify a subset of patients with MRI negative mesial epileptogenicity who could proceed directly to SAMR, potentially bypass chronic implantation of electrodes, and that these patients would have a better outcome than other MRI-negative TLE patients.

Methods: We examined a series of patients with TLE and a normal MRI who underwent acute ECoG prior to chronic implantation of electrodes and recording of ictal onsets. Based on 5 minutes of low anesthesia acute ECoG, interictal spikes were classified to be either mesial (M), lateral (L) or mesial/lateral (ML). We then correlated the results of the acute ECoG with the ultimate ictal onset zone following chronic implantation. Seizure onsets were also classified as either "M", "L" , or "ML". We further evaluated the correlation of ictal onsets with other modalities including PET, scalp-EEG, and WADA testing. Outcome was assessed with Kaplan-Meier analysis of Engel grading system.

Results: Sixteen patients fit criteria for inclusion. Eight were male (age range 20-47). Mean post-operative follow-up was 45.2 months (range 9-86 months). Of the 16 patients, nine had Engel I outcomes, two had Engel II outcomes, four had Engel III outcomes, and one had an Engel IV outcomes. Localization from scalp EEG and PET hypometabolism correlated with ictal onsets from chronic ECoG in 69% and 64% of patients, respectively. WADA memory scores correlated with onsets in 47% of patients. Acute intraoperative ECoG correlated with seizure onsets on chronic intracranial recordings in all sixteen (100%) patients. All 8 patients with "M" pattern acute ECoG went on to have a SAMR, and 6 (75%) experienced Engel I outcomes, whereas in the "L" and "ML" subgroups, only 3 of 8 patients (38%) had Engel I outcomes. There were 2 complications in 32 surgeries (6%), both associated with grid placement with no long-term sequelae.

Conclusions: Acute intraoperative ECoG may be useful in identifying a subset of patients with MRI-negative TLE who will benefit from SAMR, without requiring chronic implantation of electrodes. These patients have uniquely mesial interictal spikes on acute ECoG and will usually go on to have an excellent post-operative seizure-free outcome. Patients with any neocortical spikes or absence of mesial spikes will benefit from chronic implantation with electrodes, but may have a worse outcome.

2.307

DEPTH ELECTRODE RECORDING IN EPILEPSY SURGERY. A FIVE YEAR REVIEW

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Rationale: Depth electrode recording (SEEG) may be required as part of the presurgical workup of epilepsy patients. In this study we report our outcome data for depth electrode recording in epilepsy patients.

Methods: A prospective database was used to review all patients implanted over a 5 year period ending January 2010. Only patients who had depth electrodes inserted for extraoperative recording were included in this report. Grid, strip and intraoperative depth electrode recordings were not included in the analysis.

Results: For the 5 year period reviewed, 48 patients had a total of 384 depth electrodes inserted as part of their epilepsy evaluation. The average age of the patients was 33 years (range 5 - 55). On average 8 electrodes (range 2 - 16) were inserted for an average of 10 days (range

2 -19). Transient complications were infrequent (n=3). One patient pulled the electrodes out prematurely without consequence. One patient had a superficial skin infection requiring oral antibiotics. One patient had pulmonary edema post operatively requiring ICU admission. This patient recovered completely. The etiology of the pulmonary edema was unknown. Of the 48 patients implanted, 33 went on to have resective surgery (69%). With respect to outcome, 15/27 (56%) were Engel I, 5/27 (19%) were Engel II, and 4/27 (14%) were Engel III.

Conclusions: Invasive depth electrode recording (SEEG) is safe. In properly selected patient populations almost 70% of patients can expect some surgical solution with an Engel I outcome expected in 56% of patients.

2.308

CHANGE IN SEIZURE SEVERITY AFTER ANTERIOR TEMPORAL LOBECTOMY

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Rationale: Conventional assessment of seizure outcome after anterior temporal lobectomy (ATL) examines the effect of surgery on seizure frequency but not on seizure severity. However, for patients with persistent seizures after surgery, mitigation or intensification of seizure severity may have clinically meaningful impacts. Therefore, defining whether seizure type changes after surgery is important. We assessed whether seizure severity changes after ATL and determined whether any clinical features are associated with occurrence of secondarily generalized tonic-clonic seizures (GTCS) after surgery.

Methods: Patients who had an ATL to treat medically refractory seizures were prospectively registered in a database from 1986 through 2008. Patients eligible for this study were followed for at least five years after surgery and had adequate documentation of preoperative and postoperative seizure types and frequency. Clinical data included age at surgery, gender, side of surgery, age at seizure onset, duration of epilepsy, febrile convulsion, IQ and seizure history including pre and post-operative seizure frequency and seizure type including GTCS, complex partial seizures (CPS) and simple partial seizures (SPS). Chi square, t- tests and the modified Wald statistic were used for data analysis.

Results: 338 patients with a mean follow-up of 10.14 years (range 5-22 years) were eligible for inclusion. 173 were male, 165 were female, 178 had right ATL and 160 had left ATL, mean age at surgery was 34.7 ± 10 years, average duration of epilepsy was 19.78 ± 11 years and mean full scale IQ was 91.31 ± 13.

179 patients (53.0%) had one or more CPS or GTCS after surgery; 159 had no recurrences. The data are summarized in the table. The chance of developing de novo GTCS after ATL was 6.2% (95% CI = 3.0-11.9%). Chance of GTCS remitting if present before surgery were 65.9% (95% CI = 59.2-72.0%). Among 8 patients who had not had GTCS before surgery and developed new onset GTCS after operation, 4 (50%) had one GTCS, 2 (25%) had two or three GTCS, and 2 (25%) had > 3 GTCS. Of the 8, one had GTCS acutely (d" 1 month) and one had a seizure sub-acutely (d" 6 months).

The main risk factor for having GTCS after surgery was having GTCS in the year before surgery ($p = 0.03$). In contrast, age at seizure onset, age at surgery, FIQ, gender and history of febrile seizures in childhood were not associated with risk of GTCS occurrence after operation.

Conclusions: In addition to improving seizure frequency, ATL substantially ameliorates seizure severity in patients. It infrequently leads to de novo GTCS; even when these first appear after surgery, they are usually rare. The most striking effect of surgery is the abolition of GTCS in most patients. The mechanism may be due to interruption of networks for seizure spread or reduction in the volume of epileptogenic cortex, which may then be less able to produce seizures that are potent enough to spread to subcortical structures needed for the clinical expression of GTCS.

Table: Change in seizure type after anterior temporal lobectomy

IMAGE: tables/903746_T1.jpg

2.309

ANTERIOR NUCLEUS OF THE THALAMUS DEEP BRAIN STIMULATION (AN-DBS) IN PATIENTS WHO FAILED EXTRA-TEMPORAL OR TEMPORAL LOBE RESECTION

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Rationale: Patients with extra-temporal epilepsy and normal MRI represent a challenge for the surgical treatment. Up to 60% of them are not made seizure-free after the procedure; this is also true for 10-15% of the patients with temporal lobe epilepsy who are usually the best candidates for surgery. These surgical failures, which were medically refractory beforehand, have few therapeutic options. Neuromodulatory techniques, especially vagus nerve stimulation, have been tried over the last years. Deep brain stimulation emerged as a potentially new therapeutic option for these patients.

Methods: Six patients who failed extratemporal (n=3) or temporal (n=3) cortical resection were studied. One patient had rolandic (previously submitted to sensitive and motor giri resection), 2 had frontal (previously submitted to frontal resection and 3 had temporal (previously submitted to cortico-amygdalo-hippocampectomy) lobe epilepsy; all had unremarkable MRI findings before cortical resection. All patients were implanted bilaterally at the anterior nucleus of the thalamus (AN) using a Kinetra device. Continuous bilateral stimulation was carried out using 130Hz, 300usec, 4-6V pulses; stimulus intensity was increased every 2 weeks (0.5V increments). CT scanning checked the electrode's position postoperatively.

Results: A recruiting stimuli-driven response could be seen bilaterally over the fronto-temporal convexity after low-frequency AN intra-operative stimulation. A DC-shift was noted when high-frequency stimulation was used. The patient with rolandic epilepsy had 30% reduction in seizure frequency; those with frontal lobe epilepsy had 50 and 55% reduction in seizure frequency. Patients with temporal lobe epilepsy had 80, 80 and 90% seizure frequency reduction, respectively. Three patients presented transient (30-45 minutes) paresthesia during the programming sessions during which stimulus intensity was increased. There was no neuropsychological decline or somnolence.

Conclusions: AN-DBS proved to be safe and effective in this patient population. Although the number of patients is small for statistical

analysis, those with failed temporal lobe surgery did much better than those with extra-temporal epilepsy. These findings might correlate with the known direct projections from the AN to other Papez circuit targets (including the temporal lobe). There is no efficient direct projections from the AN to rolandic or lateral frontal cortex. Pre-study worries regarding side effects due to continuous bilateral AN stimulation did not materialized during follow-up.

2.310

LONG-TERM EPILEPSY SURGERY OUTCOME IN ARGENTINA

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Rationale: Epilepsy surgery procedures started in Argentina more than 50 years ago. This is the first comprehensive and systematic survey of epilepsy surgery long-term outcome from our country. Eighty percent of patients suffering from epilepsy worldwide live in developing countries. Epilepsy surgery now affords an excellent opportunity to suppress seizure activity, improving quality of life and outweighing risks inherent to the procedure itself.

Methods: A descriptive retrospective cohort study using information from epilepsy surgery databases was conducted. All patients operated between 1998 and 2008 for drug-resistant epilepsy was analyzed. One hundred and fifty cases were operated on, only cases with a minimum of 12 months follow-up were included (N=110). In 88 cases (80%) resective surgery was performed, and outcome periodically assessed using the Engel score. Engel's score was systematically assessed by epileptologists or neurosurgeons in follow up visits. When patients were not available for personal interview, Engel scores were obtained via telephone interview. Patients were stratified into groups according to follow-up duration as follows: 12 months, 13-36 months, 37-60 months and over than 60 months and were grouped according procedure. Standard epilepsy MRI protocol was used to study all patients. Use of Video-EEG (VEEG) monitoring prior to surgery, intracranial electrode implants, intraoperative electrocorticograms (ECoG) and Wada tests was also evaluated. Pathology reports, use of antiepileptic drugs (AEDs) before and after surgery, immediate and long-term mortality and surgical complication rates were also analyzed.

Results: Surgical techniques included: 69 lobectomies (62.7%), 15 lesionectomies (13.6%), 6 callosotomies (5.4%), 6 multiple subpial transection (5.4%), 11 vagus nerve stimulations (10%), 3 hemispherectomies (2.7%). AEDs were discontinued in 19 patients (17.3%). Mean follow-up: 46 months. Male: female ratio: 1/1.44. Mean age at time of surgery: 26.2 years. Mean duration of epilepsy: 14 years. Age at seizure onset: 11.5 years. Pathology findings: mesial temporal sclerosis 32 (36.4%); dual pathology 17 (19.3%); cortical dysplasia 15 (17%); non-specific inflammatory changes 11 (12.5%); tumours 7 (8%); other 6 (6.8%). All patients were evaluated by VEEG monitoring. Intracranial electrodes: 32 patients (29.1%), intraoperative ECoG: 34 patients (30.9%) and Wada test: 42 (38.2%). Engel scores at 12 months follow-up: 69.3% (61) class I, 15.9% (14) class II and 14.7% (13) class III-IV; 13-36 months after surgery: 68.1% of cases were class I, 15.9% class II and 15.5% class III-IV. After 37-60 months follow-up, 70.6% class I, 15.7% class II, 13.7% class III-IV. Over 60 months (n = 45) 76.3% class I, 15.8% class II and 7.9% class III-IV. No complications were observed in 97 cases (88%).

Conclusions: Conducting a successful epilepsy surgery program in a developing country is challenging. These results should encourage specialists in these countries to study this population, train specialized staff and acquire appropriate technology. Long-term outcome results comparable to centres in developed countries can be achieved.

2.311

APPLICATION OF FOCAL CEREBRAL COOLING FOR THE TREATMENT OF INTRACTABLE EPILEPSY: AN OVERVIEW OF PAST STUDIES

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Rationale: Focal cooling of the brain has the potential to terminate epileptic discharges. Brain cooling was first proposed approximately 50 years ago and it has again come into the spotlight in recent years owing to numerous technical advances. Our group has also investigated the effect of cooling on epileptic seizures over the past 8 years. Therefore, in the present report, we review our past studies and discuss the future perspectives of brain cooling as a potential therapy for patients with intractable epilepsy.

Methods: The experiments were performed on adult male Sprague-Dawley rats under halothane anesthesia. After craniotomy, the cooling device (Peltier chip) was placed on the cortical surface or inserted in the hippocampus. Kainic acid (KA) was then injected into either the cortex or hippocampus to provoke epileptiform discharges (EDs). Furthermore, the effect of cortical cooling was examined with free-moving spontaneous epileptic rats (SERs). Cortical cooling was also applied in patients with intractable epilepsy after obtaining informed consent. During surgery, cooling was performed for 20 minutes in the epileptogenic cortex, which had to be resected. Finally, the neuropathological consequences and influence on neurophysiological function due to cortical cooling were assessed in the rats.

Results: The EDs decreased in amplitude immediately after the start of cooling and then continued to decrease during either cortical or hippocampal cooling (20-25 °C) in rats. Seizures were confirmed to be suppressed in SERs. Histologically, no apparent damage was observed in the cortex after cooling above 0 °C for 1 hour. The neurophysiological functions were also preserved during cooling above 15 °C. The EDs diminished, and neurotransmitters, such as glutamate, were observed to decrease during cortical cooling (20 °C) in human epileptic patients.

Conclusions: Both the effectiveness and safety of focal cooling for intractable epilepsy were demonstrated in these studies. Based on these data, further developments in the production of implantable focal cooling device with the closed-loop system (seizure detection and focal cooling) have been promoted based on our findings, although several aspects still remain uncharacterized concerning the hardware aspects.

2.312

LONG-TERM FOLLOW-UP AFTER FRONTAL LOBE EPILEPSY SURGERY

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Rationale: Since there has been controversy in determining which cases of frontal lobe epilepsy (FLE) should be approached with resective surgery, the aim of this study is to determine the favorable prognostic factors and long-term outcome.

Methods: 71 patients diagnosed with FLE based on intracranial or scalp EEG monitoring by the Dartmouth Epilepsy Program were retrospectively reviewed. 58 patients with localizable FLE underwent resective surgery and have at least nine months of follow-up. Patient demographics, risk factors, seizure characteristics, diagnostic tests, imaging studies, and neuropsychological data were tabulated. Outcome measures (Engel, employment, seizure freedom during the last year of follow-up, and time to first recurrent seizure) were determined based upon yearly follow-up data.

Results: Of the 58 resective patients, 20 (34%) had onset in the supplementary motor area (SMA) and medial frontal region, 15 (26%) in the frontal convexity, 13 (23%) in the orbitofrontal region, and 10 (17%) in the fronto-polar region. 52 (90%) underwent intracranial monitoring. 32 (55%) patients had lesions visible on MRI. The mean follow-up period was 82.9 months (>6.5 years). 57% of the resective patients had a class I outcome (either complete seizure freedom, only non-disabling simple partial seizures, freedom from disabling seizures during the last two years of follow-up, or only seizures induced by drug withdrawal) while 72% had a class II outcome (rare disabling seizures) or better. Orbitofrontal and SMA or medial frontal patients tended to do better than other locations (table 1, p=0.06). The mean time to the first seizure after surgery was 31 months. Only 13 patients (22%) never had another event (no auras or seizures with medication changes), corresponding to an Engel IA outcome. 7% of resective patients were seizure free for at least 1 year after initial postoperative seizure recurrence (a running-down effect) and 16% experienced initial seizure freedom for at least 1 year before seizure relapse, while 28% experienced alternating periods of seizure freedom and seizure relapse. 53% of the resective patients were seizure-free during the last year of follow-up. Of the 21 patients unemployed preoperatively, 32% were employed at last follow-up while 82% of the 35 patients employed preoperatively were employed at last follow-up. Postoperative employment correlated with Engel outcome (p=0.01). Age at surgery, risk factors, pathology, and the presence of lesions on preoperative MRI scans were not associated with long-term seizure outcome (p>0.05).

Conclusions: Long-term outcome is favorable in FLE resective surgery. Though location of seizure focus is not significantly associated with outcome, the orbitofrontal and SMA or medial frontal syndromes tend to have better long-term outcomes. The lack of a significant association between the presence of a lesion on preoperative MRI scans and a better seizure outcome should be further investigated.

Engel's Outcome by Location of Seizure Onset

IMAGE: tables/890604_T1.jpg

2.313

THE USE OF VAGUS NERVE STIMULATION (VNS) IN REFRACTORY EPILEPSY PATIENTS

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Rationale: The purpose of this study was to identify and characterize the patient subgroup of ablative epilepsy surgery candidates who receive VNS rather than ablative surgery.

Background

Although vagus nerve stimulation (VNS) and ablative surgery are both indicated for medically refractory partial onset seizures, ablative surgery can provide greater seizure control than VNS in appropriately selected patients. Suitable ablative surgery candidates who receive VNS rather than ablative surgery are likely to experience suboptimal seizure control. An improved understanding of the subgroup of ablative epilepsy surgery candidates who receive VNS rather than ablative surgery could lead to improved future care for medically refractory epilepsy patients.

Methods: We queried the Medical College of Georgia epilepsy surgery database. We identified all patients who received an epilepsy surgery evaluation 1998 to 2009 with an implanted vagus nerve stimulator. We began the search in 1998, the year of VNS FDA approval. We identified the age, sex, surgery type, pathology, and 1-year post-operative outcome for these patients.

Results: Among the 700 patients who received an epilepsy surgery evaluation, we identified 51 patients with a vagus nerve stimulator who received an epilepsy surgery evaluation; 26 (51%) were males and 25 (49%) were females. Among the 51 patients, 40 (78%) patients received epilepsy surgery. Among the 40 patients, 25 patients (62.5%) had a cortical resection, 3 (7.5%) patients had a partial corpus callosotomy, 9 (22.5%) patients had a complete corpus callosotomy, and 3 (7.5%) had a hemispherectomy. There were 10 adults (age 18 to 44), and 15 pediatric patients (age 5 to 17). The one year post-operative outcome was 10(40%, Engel Class I), 1(4%,Engel Class II), 8(32%, Engel Class III),4(16%,Engel Class IV) and 2 patients were lost to follow up. Among the 25 patients, surgical pathology was neoplasm (2 patients),cortical malformation (7 patients), subpial and white matter gliosis (12 patients),and 4 patients had mesial temporal sclerosis.

Conclusions: This study indicates that a significant number of medically refractory epilepsy patients received initial treatment with VNS rather than ablative epilepsy surgery; this failure to receive ablative epilepsy surgery led to a delay in optimal seizure control. This problem was more prevalent among pediatric patients. The diverse range of seizure types and etiologies suggests a failure among practitioners to recognize the benefit of ablative epilepsy surgery as a whole rather than a failure to recognize the benefit in a specific subgroup of ablative surgery candidates. Improved education of epilepsy among practitioners could lead to improved outcome for medically refractory epilepsy patients.

2.314

INTRACRANIAL SURVEY STUDIES: USEFULNESS AND PROGNOSTIC IMPLICATIONS

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Rationale: Intracranial recording for seizure localization is invaluable in certain selected surgical patients. Comprehensive preoperative noninvasive data collection is used to generate a hypothesis about the best approach to place intracranial electrodes with the aim to further narrow and identify the epileptic focus. Despite best efforts preoperative evaluation often fails to localize or even lateralize the epileptic focus or generates contradictory results. Among such patients if a single epileptic focus is still suspected many Epilepsy Centers perform bilateral survey intracranial recording. Details about the value of such approach are limited.

Methods: Retrospective review of patients with bilateral intracranial survey studies in our Epilepsy Center with at least one year follow-up. Data collected and analyzed included demographic, clinical, preoperative evaluation, methods and results of intracranial survey recording, any interventions performed based on the results of intracranial survey and long term seizure prognosis. Patients with suspected mesial temporal lobe epilepsy with intracranial recording done to lateralize seizure focus or rule out bitemporal lobe epilepsy were excluded.

Results: 15 patients were identified (8 females). At time of survey recording patients age ranged between 2- 53 (mean 22.4 years). Average time from diagnosis of epilepsy was 8.8 years. 9/15 had bitemporal and bifrontal sampling most commonly with bilateral anterior, inferior and posterior frontal and anterior, posterior and subtemporal coverage with or without bilateral hippocampal depths. 4/15 had bilateral posterior coverage with parietal-occipital and temporal-parietal-occipital coverage. 2/15 had bilateral frontal-temporal-parietal-occipital electrode placement. Interhemispheric coverage was done in 6/15 patients. Based on the results of intracranial survey 3/15 had temporal lobe resection. All 3 were seizure free or substantially better (modified Engel classes I and II). Three patients had no further surgeries 2 due to failure of survey study to further define seizure focus and one due to multifocality. 9/15 underwent further intracranial studies mostly with unilateral subdural grid placement of those 6/9 eventually had surgical resection of seizure focus, 2 with parietal lobe resection, 1 orbitofrontal , 2 lateral frontal and 1 frontal-parietal (2 classes I- II and 4 classes III-IV) . Overall analysis shows that in our patients with intracranial survey study helpful information in further surgical planning or surgical eligibility was obtained in 86 % of the cases. Among patients who eventually had surgical resection 55 % were seizure free or substantially better.

Conclusions: Bilateral survey intracranial studies should be considered for further surgical planning in a subset of epilepsy surgery candidates. Considering the type of patients selected for intracranial survey study the procedure does not appear to imply worse long term surgical prognosis.

2.315

SEIZURE OUTCOMES AND QUALITY OF LIFE FOLLOWING CORPUS CALLOSOTOMY FOR DROP SEIZURES

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Rationale: Corpus callosotomy (CC) is a surgical treatment for medically intractable seizures, particularly of drop seizures. This treatment has been used for decades to reduce injury due to falls and generalized seizures. Evidence has been reported of decreased seizure frequency after CC; however, quality of life outcomes have not been well addressed in the current literature. It is often assumed that quality of life correlates with seizure frequency and severity. Therefore, we undertook a retrospective chart review of adult and pediatric patients who have undergone CC for medically intractable seizures to evaluate seizure outcomes. We also performed a prospective study to obtain patients'/guardians' perspective of patients' current quality of life measures.

Methods: After obtaining appropriate IRB approval, records were reviewed to identify all patients having undergone corpus callosotomy (CC) for refractory drop seizures at the Mayo Clinic between 1990 and 2009. Inclusion criteria consisted of age greater than 5 years; medically intractable seizures, including drop seizures, with no identified surgically resectable focus; and undergoing an anterior, complete, or anterior and later completed CC. Seizure types and frequency were recorded prior to and following CC in order to determine effectiveness of the procedure. Questionnaires, including the Hague Restrictions in Childhood Epilepsy Scale, the Impact of Childhood Epilepsy Scale, and the Quality of Life in Epilepsy (QOLIE-31) scale, were sent to all patients meeting inclusion criteria to assess current quality of life measures.

Results: 43 patients were identified who met inclusion criteria. Questionnaires were returned by 16 patients, with 3 patients lost to follow up. Of the 16 patients, 10 consented to participate, 4 declined, and 2 were deceased. Among the 10 consented patients, the average age of seizure onset was 3 years. CC was performed as anterior 2/3rd (6), complete (3) or anterior followed later by completion (1). Atonic seizures were significantly decreased in 9/10 patients. Average quality of life score was rated as 4.3 on the 7-point modified Rankin scale, and 5.6 on the 10-point QOLIE-31 scale. Average overall health score was rated as 1.4 on a 4-point scale, and 5.6 on the 10-point QOLIE-31 scale. Average self esteem score was rated as 1.3 on a 4-point scale. Four of the 10 patients reported worsened cognitive or behavioral status following CC. Quality of life for this group was slightly worse (3.8 +/- 1.3), than the group not reporting changes (4.7 +/- 1.9).

Conclusions: Corpus callosotomy is an effective surgical treatment for refractory drop seizures, resulting in a decrease in this seizure type in nearly all patients in this study. For these patients, on average, current quality of life after CC is reported as moderate. However, a trend was noted, although not significant, of a relationship between quality of life and cognitive outcomes, suggesting that worsened cognitive outcomes contributed to reporting a lower quality of life, despite improvement in drop attacks.

2.316

CLINICAL USE OF FUNCTIONAL MAGNETIC RESONANCE IMAGING FOR CLEARING BRAIN AREAS FOR RESECTIVE SURGERY

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Rationale: Prior to resective brain surgery it is important to know that areas to be resected do not carry important function. The gold standard for clearing brain areas for resection involves invasive electrical stimulation mapping (ESM). Functional magnetic resonance imaging (fMRI) may be a tool to help perform this noninvasively. To our knowledge this approach has not been formally tested on its validity to predict ESM results, particularly on its potential clinical utility as a tool to clear brain areas for function. We investigate the spatial correlation of ESM results with the blood oxygen level-dependent (BOLD) response for language and motor tasks. This study aims to define the role of fMRI to delineate areas that should be spared from resection.

Methods: fMRI was recorded while patients were doing a finger tapping task (N=8) or a picture naming task (N=5). ESM was performed with analogous tasks for language mapping. Post-implantation CT was coregistered to the pre-implantation fMRI using an automated method that accounted for brain shift and the craniotomy. With this coregistration, the BOLD response in the vicinity of electrodes was correlated with the results of ESM. 262 electrodes sites were investigated for language function and 473 for motor function. Sensitivity, specificity and predictive values were calculated for validation of fMRI. We used different region of interest volumes (ROIV) under the electrodes to maximize negative predictive value (NPV) and examined the correlation of expressive and receptive language functions separately.

Results: Significantly higher t-scores were associated with ESM positive electrodes compared to ESM negative electrodes for both, motor (5.9 vs. 3.0; $p<0.01$) and language (2.3 vs. 1.6; $p<0.01$) functions. At a t-score threshold of 2.5, and a ROIV of 16mm the sensitivity and negative predictive values are both above 99%, which is excellent for clinical use. Using the same parameters language showed NPV that would not be sufficient for clinical utility (< 85%). Including only expressive language areas the NPV increased to a clinical useful value of 99% and the sensitivity to 97%.

Conclusions: fMRI may localize expressive language function with the same accuracy as motor function, which reaches a clinically useful degree. Using conjunct analysis of several language tasks as well as additional post-hoc analysis might provide better results for global analysis of language.

2.317

IS ADDITIONAL AMYGDALO-HIPPOCAMPECTOMY NECESSARY FOR INTRACTABLE LESIONAL TEMPORAL LOBE EPILEPSY?

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Rationale: It is controversial whether amygdalo-hippocampectomy (AH) in addition to the lesionectomy would result in better outcomes for intractable temporal lobe epilepsy associated with temporal lesions. In this study, we retrospectively review the surgical outcomes of lesional temporal lobe epilepsy.

Methods: From 2000, 13 intractable temporal lobe epilepsy patients, who had temporal lesions in MRI, underwent surgical treatments of our department. Pathologies included 5 gngliogliomas cases, 5 cavernous angiomas, one astrocytoma Gd II, one dysembryoplastic neuroepithelial tumor (DNT) and one arachnoid cyst. Four patients had choronic subdural electrode studies. AH and lesionectomy were selected in 3 ganglioglioma cases located in non-dominant parahippocampal gyri and one arachnoid cyst located in the non-dominant middle fossa. In the other 9 cases, lesions were located in the dominant temporal lobe. In these cases, lesionectomy (some cases with surrounding cortex removed) without AH were performed, even if FDG-PET or intraoperative electrocorticography suggested secondary epileptogenicity in the hippocampus. They were followed for more than two years after surgery.

Results: Eleven cases resulted in Engel's class Ia. One non-dominant ganglioglioma case with AH resulted in class Ic and one dominant DNT case without AH resulted in class Ib.

Conclusions: We found no evidence to support the idea that lesionectomy with additional AH for lesional temporal lobe epilepsy would result in better outcomes when compared to lesionectomy alone, especially in cases of dominant side.

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Surgical strategy for lesional temporal lobe epilepsy

2.318

PLANNING INTRACRANIAL ELECTRODE STUDIES FOR SEIZURE LOCALIZATION IN CASES OF NONLESIONAL NEOCORTICAL EPILEPSY

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Rationale: Nonlesional neocortical resections result in freedom from seizures in approximately half of patients. However, noninvasive studies and the design of invasive electrode surveys vary among centers. Here we describe our approach to planning invasive electrode studies for nonlesional neocortical epilepsy.

Methods: We reviewed intracranial electrode studies for nonlesional neocortical cases from 2005-2010. The impact of noninvasive studies on invasive electrode plans was assessed, and common survey strategies were identified.

Results: The routine set of noninvasive studies included a detailed history and neurological examination, neuropsychological testing, anatomical magnetic resonance imaging (MRI), continuous audiovisual-electroencephalography monitoring (CAV-EEG), positron emission tomography (PET), interictal single positron emission computed tomography (iiSPECT), 7T magnetic resonance spectroscopy (MRS), ictal SPECT (iSPECT), and the Wada test. Functional MRI (fMRI) and spike-triggered fMRI were obtained in many patients. Factors that typically guided the design of intracranial electrode studies were seizure semiology, ictal CAV-EEG, neuropsychology, iSPECT, and language lateralization. PET and iiSPECT results less commonly affected electrode implantation, while MRS and spike-triggered fMRI were treated as investigational studies with minimal impact on decision-making.

Intracranial electrode surveys were designed to cover the neocortex broadly, with denser sampling guided by noninvasive studies. Noninvasive studies sometimes lateralized seizure onset, but bilateral studies were common, especially with frontal lobe semiology and electrographic findings. Craniotomies were positioned to cover the cortical regions hypothesized to be the origin of seizures. All craniotomies included subdural strip electrodes extending radially from

the perimeter of the craniotomy in a starburst pattern. When frontal lobe seizures were suspected, interhemispheric placement of bilateral medial strip electrodes from the nondominant side was included. Subdural grid electrodes were included when a certain region was highly suspicious or when stimulation mapping was planned. Electrode arrays were typically supplemented with one to three depth electrodes per side. Depth electrodes were placed in the bilateral hippocampi or frontal lobes, or were targeted to an iSPECT focus. Depending on results from the intracranial survey, a second localized intracranial study was often undertaken with subdural grid electrodes overlying the seizure origin and areas requiring stimulation mapping for resection planning.

Conclusions: Details of current approaches for designing intracranial electrode studies are not widely known, and there is little evidence for choosing between approaches. The findings presented here illustrate the current approach at Yale. Quantitative comparison among approaches likely will be necessary to determine the optimal approach to localizing neocortical epileptic foci.

2.319

A MINIMAL INVASIVE SURGICAL APPROACH: THERMOABLATION FOR AN ISOLATED PERIVENTRICULAR NODULAR HETEROTOPIA

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Rationale: Ictal onset in an isolated periventricular nodular heterotopia (PNH) has already been demonstrated in 1998 (Kothare et al., Neurology 1998;51:1723-1727). PNHs can be connected to the overlying cortex, so that lesionectomy and partial cortectomy seems to be an optimal therapeutic approach. However, this procedure has considerable limits in patients with adjacent functional eloquent cortex or with multiple PNH, so that a surgical procedure is oftentimes dismissed.

Methods: We attempted a far less invasive approach with stereotactically guided thermoablation after ictal recordings with surface and depth electrodes suggested the epileptogenic zone at the isolated PNH. Postsurgical follow up was assessed every six months.

Results: This 56-year-old otherwise healthy man experienced unspecific auras, clonic, aphasic, dialeptic and bilateral tonic-clinic seizures since the age of three. Before operation the seizure frequency was 1-2/day for the simple and partial seizures and 1/week for the grand-mal, respectively. After the surgical interventions there was one cluster of breakthrough seizures after accidental non-adherence to antiepileptic medication.

Conclusions: We present a case with a favorable outcome after minimal invasive epilepsy surgery. Thermoablation should be considered in the case of concordant surface and stereo-EEG findings. For certain patients with multiple PNH, thermoablation could also be considered prior to resective surgery.

IMAGE: images/904366_A.jpg

IMAGE: images/904366_B.jpg

2.320

MORTALITY AFTER EPILEPSY SURGERY

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Rationale: We previously found that excess mortality from epilepsy was reduced in patients who became seizure free after surgery whereas patients with persistent seizures had high mortality rates. We further explored the effect of seizure control, location of focus, and epilepsy syndrome on late postoperative mortality in a much larger sample of patients.

Methods: Patients were assessed for seizure control and survival after epilepsy surgery including resection, callosotomy and vagus nerve stimulation (VNS). Data was registered in a prospectively maintained database, and mortality was assessed by direct patient contact and review of the Social Security death index. After surgery, patients with no seizures or only auras were termed seizure-free, and those who had any seizures with altered awareness were termed as having recurrent seizures. The censoring date was 7-15-09 and data was truncated at 15 years of follow-up to maintain model validity. Kaplan-Meier curves were generated, groups were compared using the Cox-Mantel test, and death rates were computed based upon person-years of follow-up.

Results: 1011 patients were eligible for analysis. There were 526 males and 485 females, mean age at surgery was 35 years, mean age of onset was 14.7 years, and mean IQ was 89.

855 patients had resective surgery; only one of 326 seizure-free patients died, whereas 44 of 529 patients with one or more postoperative seizures died after surgery ($p < .001$) (Figure 1). The death rate was 8.48 per 1000 person-years (95% CI: 6.16-11.39) in patients with postoperative seizures after resection. Callosotomy patients with recurrent seizures (n=101) had a non-significant trend to have higher mortality rates (13.7 per 1000 person-years [95% CI: 7.29-23.43]) than resection patients with recurrent seizures ($p = .12$) (Figure 2). Mortality was similar for patients with seizure recurrence after temporal (n=381) and extratemporal resection (n=125). Approximately half of the deaths were due to probable SUDEP in cases when cause of death could be ascertained. All deaths in resection patients were unrelated to the surgical procedure and represented late mortality; there was 1 perioperative death among the callosotomy patients (n = 106, total 13 deaths).

No VNS patients were seizure-free (none had brain surgery), and their mortality rate was 12.29 per 1000 person-years (95% CI: 3.98-28.69), with 5 deaths observed in 50 patients. VNS and resective surgery patients with recurrent seizures had similar mortality rates.

Conclusions: Patients who are seizure-free after epilepsy surgery have low mortality rates indistinguishable from the general population, consistent with the hypothesis that surgery reduces excess mortality from epilepsy. Mortality from epilepsy remains high if seizures persist after either brain surgery or VNS, despite any reduction in seizure frequency. Limbic foci do not appear to increase risk of mortality. The greater burden of neurological disease in callosotomy patients, who mostly have symptomatic generalized epilepsy, may confer increased risk.

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Graph showing survival over 15 years after resective surgery for epilepsy (temporal and extratemporal). Only 1 of 326 seizure-free patients died, whereas 44 of 529 patients who had recurrent seizures died after resective surgery ($p < .001$).

IMAGE: images/906047_B.jpg

Graph showing a trend for higher mortality in callostomy patients than resective surgery patients. This likely reflects a greater burden of neurological disease in the callosotomy population, who mostly have symptomatic generalized epilepsy.

2.321

NEW MICRO CRYOGENIC PROBE AS NEW FACILITIES FOR BRAIN SURGERY

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Rationale: Cryogenics is used as a powerful tool in therapy (cooling) and surgery (freezing) of the brain. However, the application field of cryogenics is mainly restricted by the surface of the brain. Cryogenics still does not possess a specific feature of radiation surgery, because regular cryogenic probes cannot penetrate deep inside the brain without the risk of damage to nearby healthy tissue. We aim to ensure the feasibility of using cryogenic exposure in the depths of the brain to destroy abnormal or diseased tissue with minimal damage to the nearby healthy neurons. In this study, the new micro cryogenic probe has been developed specifically for the brain surgery. The micro probe is capable of a deep freeze at its very tip while the main part of the probe is heat-insulated and does not affect the tissue.

Methods: The method of freezing is based on the phase transition - liquid refrigerant is boiling inside of the cryogenic probe. The silver tip at the end of the probe provides a good heat contact between the inner and outer sides. The rest of the probe surface has a thermal isolation. The combination of a silver tip and thermal isolation, provides the cryogenic probe with a high freezing rate at its tip, while the main part of the probe does not affect the healthy tissue during the operation. Commercially available refrigerant with a boiling point of -50^{o}C is used in the experiment. Since the phase transition is a natural stabilizer, freezing temperature is maintained a constant with high accuracy. The dimensions of the probe were chosen equal to or less than the electrodes used in neurosurgery, and ranged in outer diameter from 0.7 mm to 2.5 mm.

Results: The cryogenic probe with a diameter of 0.7 mm was used to monitor the freezing of a mixture of agar and gelatin gels. The temperature of the mixture was maintained at 36.6^{o}C by means of water bath. Once freezing starts, an ice ball is gradually growing during about 5 minutes and then becomes stable when reaching the size of about 4.5 mm, as is seen in Figure1. As is evident from the theoretical model, the ice ball dimension depends on probe diameter and boiling point of the refrigerant. For the given boiling point of refrigerant and probe diameter, the experimental result is in good agreement with theoretical estimation. A similar experiment was performed with the rat brain *in vivo*. Two weeks after freezing, the rat brain was extracted and sliced for examination. As seen from Figure 2, size of ablated area of the brain correlated with the frozen gel ball.

Conclusions: A new reliable cryogenic probe that satisfied the rigid conditions of neurosurgery has been developed. The probe is able to ablate by means of freezing a specified volume deep inside of the brain without cryogenic damage to healthy tissue. Minimally invasive treatment is caused by the small diameter of the probe and proper thermal isolation of its passive part.

IMAGE: images/889382_A.jpg

IMAGE: images/889382_B.jpg

2.322

TEMPOROMANDIBULAR DISORDERS FOLLOWING CRANIOTOMY FOR REFRACTORY EPILEPSY: A PROSPECTIVE EVALUATION

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Rationale: We prospectively evaluated (pre and postoperatively) the signs and symptoms of temporomandibular disorders (TMD) in patients who underwent craniotomy for refractory mesial temporal lobe epilepsy (MTLE).

Methods: We investigated 24 patients (mean age 37.3 ± 10 years; 17 women) who underwent surgery for MTLE. We used the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) to investigate pre- and post-operatory signs and symptoms of TMD, mandibular function and masticatory muscles pain. Maximal mouth opening (MMO), protrusion and laterality were also obtained. We obtained the ratio (pos-op value/pre-op value) to evaluate the relationship with preoperatory conditions. We performed paired and unpaired T-test and Fisher's exact test for statistical analyses.

Results: Presurgery, nine patients had TMJ disc displacement (DD); 15% subjects had TMJ pain; 20% patients presented masticatory muscle complaints. MMO significantly reduced after surgery ([pre-op 44.6±6.68mm],[post-op 33.4±9.47mm], $p< 0.0001$); as well as protrusion ([pre-op 6.8±1.6mm],[post-op 1.2±0.74mm], $p< 0.05$). The MMO ratio was reduced in patients with preoperatory disc displacement ([DD positive ratio 0.7±0.2],[DD negative ratio 0.86±0.08], $p=0.036$).

Conclusions: Patients with preexisting TMJ dysfunction signs undergoing craniotomy are likely to present significant worsening of the TMJ and masticatory muscles dysfunction postsurgery and neurologists should be aware of this risk.

2.323

EVALUATION OF THE FREQUENCY AND CLINICAL IMPORTANCE OF ELECTRICALLY-INDUCED SEIZURES BY USING INTRACEREBRAL AND SUBDURAL ELECTRODES

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Rationale: This study evaluates the frequency of seizures induced by electrical stimulation of the cortical and intracerebral regions, and determines the sensitivity and specificity of the induced secondary generalized seizures (SGSs), complex partial seizures (CPSs), and simple partial seizures (SPSs).

Methods: In a consecutive 62 patients with implantation of subdural and intracerebral electrodes, we performed functional mapping studies

of 52 patients and evaluated the data of 2074 and 2734 contact points in the left and right cerebral hemispheres, respectively. We conducted 7546 unifocal or bifocal stimulations trials for 275 days. The stimulation parameters were as follows: pulse duration, 0.2 ms; stimulus frequency, 50 Hz of alternative electric current; and stimulus train duration, 2-5 s. In all cases, we began mapping with 1 mA and increased the current until functional changes or afterdischarges occurred, or we increased the current till it attained the maximum intensity of 10 mA.

Results: The frequency of spontaneous seizures in 40 patients was 4 times that of induced seizures, i.e., in a total of 1129 seizures, we observed 86 SGSs, 377 CPSs, and 666 SPSs in 23, 33, and 25 patients, respectively. The electrical stimulation elicited 277 seizures in 40 patients; this frequency was 3.7% of all the stimulation trials. SGS was elicited in 28 seizures (0.37%) of 14 patients, CPS in 47 seizures (0.62%) of 16 patients, and SPS in 202 seizures (2.7%) of 30 patients. The positions of 185 and 92 electrodes that induced seizures were within and beyond the resected region, respectively. Assuming that the postsurgical outcome is good after resection of all the seizure-inducing electrodes, the sensitivity and specificity of the induced SGSs, CPSs, and SPSs were 92% and 13%, 59% and 90%, and 69% and 56%, respectively. The frequency of the induced seizures not correlated to the seizure-related zone was 14%, 74% of which was observed around the pre- and post-central gyri.

Conclusions: The induced generalized seizure showed a low frequency (0.37%) during the brain stimulation study. The clinical importance of the stimulation-induced seizure is that the specificity of CPS induction is higher than that of SPS and SGS. Although the seizure-induced region is not always included in the seizure-onset zone, the electrical stimulation study plays a partial role in the detection of excitability in the epileptogenic zones and facilitates the identification of the seizure-propagation pathways.

2.324

CORPUS CALLOSOTOMY FOR MEDICALLY REFRACTORY EPILEPSY SECONDARY TO CONGENITAL BILATERAL PERISYLVIAN SYNDROME

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Rationale: Congenital bilateral perisylvian syndrome (CBPS) is a neurological syndrome characterized by pseudobulbar palsy, cognitive deficits and bilateral perisylvian polymicrogyria. Epileptic syndromes in CBPS are often variable and the seizures are poorly controlled in 65%. Seizure reduction was accomplished by corpus callosotomy in three cases of medically refractory epilepsy secondary to CPBS.

Methods: All three cases had been aggressively treated by epileptologists with multiple anti-epileptic drugs (AEDs). However, most of the AEDs did not give patients any remarkable benefits in seizure reduction. Then corpus callosotomy was carried out for these three cases.

Results: [Case 1] A 42-year-old woman with moderate mental retardation was referred to our epilepsy center because of frequent seizures that seriously affected her daily life. Drop attacks with tonic seizure started at the age of nine and atypical absence came to her when she was fifteen years old. Epileptologists tried many kinds of AEDs to control her seizure events. However, AEDs did not work well for her. An MRI demonstrated typical bilateral perisylvian polymicrogyria. Long-term video-EEG monitoring was also performed and the final diagnosis of Lennox-Gastaut syndrome was made. Then the patient underwent anterior four fifths corpus callosotomy and showed satisfactory outcome, especially in drop attacks and periodic spasms.

[Case 2] A mentally retarded 31-year-old man with CBPS was referred to our hospital for intractable epilepsy. An exam showed left sided hemiparesis and mild dysphagia. The patient demonstrated drop attacks of generalized tonic seizures. Then complete corpus callosotomy was performed and gave the patient seizure reduction. Adjustment of AEDs is necessary because he still has frequent simple partial seizures.

[Case 3] A 13-year-old girl had been treated by pediatric epileptologists at our epilepsy center. She has left sided hemiparesis and pseudobulbar palsy, which were found when she was an infant. Her tonic spasms started at the age of nine. She fell down with these tonic spasms. An MRI also demonstrated typical bilateral perisylvian polymicrogyria. She underwent anterior four fifths corpus callosotomy, which demonstrated significant seizure reduction. Although she still has tonic spasms, she does not have clusters of the spasms at the moment.

Conclusions: Corpus callosotomy was effective for seizure reduction, particularly in drop attacks secondary to CBPS. However, these patients are not completely seizure free at present. Some of the further investigations were carried out in these patients using dense-array EEG, which showed possible foci in two of the three patients. Then we will make a plan for resective surgery or vagus nerve stimulation eventually.

2.325

EARLY POSTOPERATIVE ANTIEPILEPTIC DRUG WITHDRAWAL IN SEIZURE-FREE MESIAL TEMPORAL LOBE EPILEPSY PATIENTS WITH CONCORDANT EPILEPTOGENIC ZONE

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Rationale: Long-term cost and adverse effects due to postoperative anti-epileptic drugs (AEDs) use are of concern in patients who have achieved seizure freedom by surgery. The aim of this study is to determine whether early AED withdrawal is possible in a select patient group presenting with mesial temporal lobe epilepsy (MTLE) and concordant epileptogenic zone (EZ) from standard presurgical evaluations.

Methods: This retrospective study evaluated 317 pharmacoresistant MTLE patients who underwent anterior temporal resection from 2004 to 2008. Patients (n = 148) selected in this study had both unilateral hippocampal sclerosis determined by MRI and were seizure-free after surgery (Engel class Ia). In addition, patients (n = 67) met the criteria for high concordance in localizing the EZ as defined by congruence in clinical semiology, interictal EEG, ictal EEG, and high-resolution MRI using epilepsy protocol. We categorized the patients into 3 groups according to the time period between surgery and withdrawal from AEDs: (A) 6 months, (B) 1 year, and (C) 2 years. Patients were subsequently followed-up from 6 to 51 months (mean 46.2 months) after the start of AEDs withdrawal to determine if they maintained seizure freedom. Kaplan-Meier method was used to analyze the primary end point of recurrent seizures. Recurrence-free survival was

measured from the date of AEDs withdrawal to the date of relapse. Log-rank test was used to compare recurrence-free survival curves.

Results: A total of 67 patients were found to meet the criteria of being seizure-free, having HS, and concordant in all four diagnostic tests. Within this sub-group of patients, 26 were in group A, 12 in group B, and 18 in group C. Eleven patients were maintained on AEDs and not included in the analysis. There were no significant differences in age, gender, age of seizure onset, lateralization of EZ, and surgical procedure among the 3 groups. Throughout the follow-up period, 88.5%, 91.7% and 88.9% of patients remained seizure-free in group A, B and C, respectively. No significance was noted in recurrence-free survival curves among the three groups ($p = 0.933$).

Conclusions: In MTLE patients with highly concordant EZ, the risk for seizure relapse after surgery appears to be no greater for those who withdrew AEDs at 6 months than for those who withdrew at either 1 or 2 years after surgery. AED withdrawal at 6 month postoperatively should be possible in seizure-free MTLE patients who have highly concordant presurgical evaluations. In developing countries with limited resources, these results may be beneficial in epilepsy care management.

2.326

DEVELOPING A SYSTEMATIC TEAM APPROACH TO MONITOR, MEASURE, MODIFY AND IMPLEMENT SAFETY IN THE EMU

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Rationale: The AES Expert Consensus on EMU Patient Safety identified "a need for the creation of standards in patient care and safety measures in EMUs across the U.S.". Very few studies have documented the EMU-associated risks and provided solutions to address safety challenges. We present our EMU safety data and describe changes in EMU practices that improved patient safety.

Methods: We reviewed the Safety Assessment Database developed at Henry Ford Hospital EMU to monitor adverse outcomes such as falls, missed seizures by the EMU monitor, delayed nurse response, failed alarms, non functioning resuscitation equipment, lack of restraints when needed, suboptimal EEG recording and delay in medication administration. All the incident video-EEGs are saved for root cause analysis. EMU falls are monitored daily by the hospital and a report is generated weekly. We used the Monitor, Measure, Modify and Implement approach to identify gaps, opportunities for improvement and implement new tools to address safety.

Results: From 2007 through 2010, 854 patients (344 of which for presurgical work-up) were admitted for 5332 monitoring days. Despite 24-hour patient surveillance by EEG techs and Medical Assistants, we had a total of 15 falls one of which resulted in a fracture of the clavicle and 30 missed seizures without serious sequelae. We had 2 patients with ictal asystole, and 2 with status epilepticus due to medication withdrawal. We had no vertebral fractures, no dental injuries, no aspiration pneumonia and no deaths. We attributed the increased rate of falls to inconsistencies in applying and reinforcing preventive fall measures and missed seizures to inadequate alertness of the EMU monitors. In 2009 we launched the EMU Safety Initiative that included identification of patients at higher risk for falls; falls contract signed by the patient or caregivers to highlight the risk of falls and the preventive measures; direct supervision at all times when patients are in the bathroom or exercise; weekly EMU fall report; recruitment of entry level EEG techs for patient surveillance after-hours; outside the room charting by nurses; and round-the-clock nursing rounds to assess Pain, Personal needs, Pulmonary Hygiene, Position, Possessions, Place (6Ps); continuous education of medical, nursing, EEG tech staff. We had 11 falls and 26 missed seizures prior to implementation of the new measures and only 4 falls (no falls in 9 consecutive months) and 4 missed seizures following our Safety Initiative that resulted in 63.3% reduction in falls and 84.6% fewer missed seizures.

Conclusions: Increased awareness about EMU safety, intensive education of the epilepsy team and implementation of new practices helped us reduce the average fall rate of 3.07 per 1000 bed days to 2.28. Continuous review of safety practices in the EMU provides many opportunities for improvements by modifying current unsafe practices and implementing tools to obtain tangible positive outcomes. By developing national EMU safety benchmarks, we work towards safer EMUs and potentially establishing accreditation of EMUs similar to the Stroke Units.

2.327

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS), NATIONAL INSTITUTES OF HEALTH (NIH), COMMON DATA ELEMENT (CDE) PROJECT: VERSION 1.0 OF EPILEPSY CDES AVAILABLE FOR USE

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Rationale: To assist investigators conducting clinical studies and accelerate data sharing, the NINDS with its contractor, KAI Research, Inc., continues to foster the Common Data Element (CDE) Project, an initiative to harmonize data collection across studies. At the past two American Epilepsy Society Annual Meetings, the Project convened a Working Group of experts in epilepsy clinical research to advise the Institute on the development of Epilepsy CDEs and accompanying resources. The initial development phase of the Epilepsy CDEs is almost complete and the CDEs will be posted to the NINDS CDE Website (http://www.commondataelements.ninds.nih.gov/) for public use in July 2010.

Methods: The forty-member Epilepsy CDE Working Group (WG) divided into subgroups who met periodically to identify and define elements for the data domains of: comorbidities, neurological examination, anti-epileptic treatments, seizures and syndromes, surgery and pathology, neuropsychology, quality of life, imaging, and electrophysiology. The CDE recommendations drafted by the subgroups were then vetted through the full WG. The resulting recommendations include the following resources: Catalog of approximately 550 Epilepsy CDEs with detailed specifications for each CDE; Library of 20 customizable case report form (CRF) modules; List of about 60 standardized instruments with explanations of when each instrument is recommended for use, a summary of the instrument's strengths and weaknesses, and additional references. Version 0.0 of the Epilepsy CDEs was posted on the NINDS CDE Website for public review in June 2010. During the public review period select organizations and the larger epilepsy clinical research community will be asked to provide feedback about the Epilepsy CDEs. Then the Epilepsy CDE WG will have a chance to review the comments received during public review, make revisions to the Epilepsy CDEs, and finalize Version 1.0. Version 1.0 of the Epilepsy CDEs will then be published on the NINDS CDE Website by the end of July 2010.

Results: The poster presentation will provide an update about the status of Version 1.0 of the Epilepsy CDEs, including: Report of those researchers who have already begun to use the Epilepsy CDE; Examples of how feedback from the research community was used to improve the Epilepsy CDEs; Explanation of how the CDEs, CRF modules, and recommended instruments can be used by a clinical study; and Summary of next steps to ensure the Epilepsy CDEs meet the evolving needs of epilepsy researchers.

Conclusions: The NINDS strongly encourages investigators conducting epilepsy clinical studies to use the Epilepsy CDEs and to submit their comments about them via the NINDS CDE Website. The best way to ensure the Epilepsy CDEs are useful tools and the CDE Project accomplishes its goals is to continuously revise and add to the CDEs based upon the feedback of researchers.

2.328

THE FEASIBILITY OF PROVIDING TELE-EPILEPSY SERVICES ON THE INDIAN RESERVATION

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Rationale: A major barrier for epilepsy patients living in rural areas is the ability to access specialist care regularly. Epileptologists from The University of Arizona travel to the Hopi Health Care Center (HHCC), an IHS hospital in Northern Arizona, for one day every three months. Transportation, weather, and scheduling problems limit the number of HHCC epilepsy patients seen by the visiting neurologists during those rare occasions. Such barriers to reasonable access impose restrictions on the ability of the specialist to provide regular quality care and hamper patients' ability to self manage their epilepsy, adding to the increased risk of poor physical and mental health, poor psychosocial function, and diminished quality of life. These challenges faced by both specialists and patients under such conditions only serve to alter the clinical consultation from a regular check-up to a stressful and condensed consultation. The goal of this project is to determine the feasibility of improving continuity of epilepsy care through tele-epilepsy by determining whether patients are satisfied with the telemedicine experiences and whether patients in this minority group are accepting of telemedicine as a form of consultation.

Methods: Patients identified as having epilepsy by the HHCC were approached by their community health representatives (CHRs) and informed about the study and asked to participate. Informed consent was obtained by the CHRs. Demographic information and the Quality of Life in Epilepsy (QOLIE-31) questionnaires were obtained prior to the initial tele-epilepsy consultation visit. The CHRs at the HHCC scheduled telemedicine consultations within 3 months and then every 3 to 6 months afterwards. After each telemedicine encounter a 9 item Visit Specific Satisfaction Questionnaire (VSQ 9) was completed. In the second six months of the study, 20% of patients and their caregivers were invited to take part in an interview via telephone or in person to explore further the benefits and drawbacks of having additional epilepsy related telemedicine services as well as the process itself.

(IRB approval obtained through University of Arizona & Phoenix Area Indian Health Services.)

Results: To date, a total of 13 patients have been recruited for the study. The tele-epilepsy consultations have been well received by the Hopi patients who view the experience as novel and interesting. Overall they do not feel that the experience is impersonal and feel that the quality of care that they receive via the tele-epilepsy experience is equal to that of the in person clinic visit.

Conclusions: The patients viewed the telemedicine experience as an acceptable and reasonable supplement or replacement to the in person visits, and reported satisfaction with the epilepsy related care. Patients showed a willingness to participate in future telemedicine clinics and expressed satisfaction with the use of the telemedicine approach demonstrating that tele-epilepsy services on the Indian reservation are a feasible and acceptable option.

(Supported by a grant from the National EpiFellows Foundation to Kendra Drake, MD.)

2.329

DEVELOPING A FUNCTIONAL STATUS DIARY (FSD) FOR EPILEPSY

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Rationale: There are few validated measures to evaluate humanistic outcomes in epilepsy and none which meet the guidance recently released by the FDA. We developed a patient-reported outcome (PRO) measure intended to be sensitive to changes in functional status and suitable for daily administration in clinical trials of new medications for epilepsy.

Methods: The Functional Status Diary (FSD) for epilepsy was developed in accordance with the FDA PRO guidance, including the involvement of patients throughout the process. We used a two phase development process with the first phase presented here. Epilepsy specialists provided clinical input. Patient focus groups were recruited and conducted that targeted newly treated and drug resistant (refractory) patients with partial-onset seizures. Patients were asked to describe all aspects of functioning impacted by their epilepsy and to identify functional improvements anticipated with a significant reduction in seizure frequency. Based on the focus group results, items were drafted and refined through two iterative sets of cognitive debriefing interviews conducted with 17 additional patients.

Results: Seven focus groups (n=46) were conducted in three geographic locations. Seventy percent of the patients were white, 59% were female, and the average age was 36 years (range 19-65 years); 19 were diagnosed with depression, and 9 with anxiety. All patients reported considerable impact from epilepsy. Specific constructs associated with an anticipated 50% reduction in seizures included increased independence; reduced worry; ability to do more in work, family, and social activities; reduced emotional fluctuations; more energy; better self-esteem; and improved short-term memory. Among these constructs, we selected those which would be mutable within the duration of a trial; could be collected daily along with seizure diary data, and were consistently identified by patients. Three items meeting these criteria were selected for inclusion in the FSD: 1) How would you rate your epilepsy-related worry? 2) How would you rate the extent to which epilepsy limited your ability to do what you needed to do? 3) How would you rate the extent to which epilepsy limited your ability to do what you wanted to do? Each item utilizes a 24-hour recall period and a 0-10 numeric rating response scale. Patients in debriefing

interviews agreed that these items were highly relevant and easy to understand.

Conclusions: This FSD addresses functional impacts which are applicable across a broad spectrum of patients with partial-onset seizures despite significant heterogeneity in this patient population. The second phase of development of the FSD will evaluate its psychometric properties and association with seizure frequency in a clinical trial.

2.330

USING CONCOMITANT REMOTE CARDIAC TELEMETRY TO ENHANCE PATIENT SAFETY IN THE EPILEPSY MONITORING UNIT (EMU)

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Rationale: Patients admitted for video-EEG monitoring should be monitored continuously due to concerns for injury or cardiac/ respiratory events caused by seizures (1). For a community hospital, it is a challenge to find the resources to have qualified staff continuously monitor these patients. We hypothesized that cardiac telemetry technologists could be trained to provide video monitoring, and that remote cardiac telemetry would provide an additional layer of safety in monitoring for potentially life-threatening events.

Methods: The technologists were given 1 hour of education: explanation of role, when to call the nurse, and were shown video examples of seizures. The technologists were asked to visually check patients on the video monitors once every 5 minutes to ensure that they appeared safe and were not having a generalized tonic-clonic seizure. We surveyed the technologists after 3 months using a 5-point scale to assess: educational needs, expectations, comfort with role, overall EMU safety, and RN responsiveness. We also performed a retrospective review of the medical record and telemetry communication record for all elective patient admissions to the EMU from March 2009 thru March 2010. We collected the following information: cardiac telemetry rhythm and rates, calls from technologists to nursing staff, discharge diagnosis, and consults.

Results: The 3 month survey indicated the technologists felt they did not need additional education; most were clear on their expectations and comfortable in their role. Most felt they were contributing to patient safety. They were concerned that RN responsiveness to their calls needed to improve and how to balance other duties. Nurses were called for: 12 suspected seizures, sometimes assisted by cardiac rhythm changes; 10 episodes of unsafe behavior; and 24 episodes of being off camera without notification. There were 2 patient falls, but neither patient was on camera. Fifty-one patients were electively admitted to the EMU. Sixteen patients (31.4%) were found to have significant rate or rhythm changes. 3 of these patients had complex partial or simple partial seizures, 7 patients had non-epileptic events (including primary cardiac events), 3 patients had both epilepsy and non-epileptic events, and 3 patients had no clinical events. Five patients had ictal tachycardia (9.8%), which triggered calls to nursing staff that alerted them to seizure onset. Cardiology consultation was obtained on 4 patients.

Conclusions: Using concomitant cardiac telemetry monitoring has successfully contributed to patient safety in the epilepsy monitoring unit. Technologists were successfully trained in simple video assessment for safe vs. unsafe behavior. Remote cardiac telemetry allowed the detection of ictal arrhythmias in real time, prompting immediate assessment by nursing staff, and at times alerted nursing staff to the onset of a seizure prior to other clinical signs.

1) Noe KH, Drazkowski JF 2009. Safety of long-term video-electroencephalographic monitoring for evaluation of epilepsy. Mayo Clin Proc 84(6):495-500.

2.331

EPILEPSY ON YOUTUBE: A REVIEW OF 100 VIDEOS

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Rationale: Internet social networking sites are increasingly used as a source of medical information. The video sharing site YouTube is reported to have over 1 billion visitors per day, demonstrating great potential power to educate about medical conditions including epilepsy, but also to proliferate negative stereotypes. For highly stigmatized conditions like epilepsy, posting of videos without consent could serve as a source of potential harm. A 2010 review of 10 epilepsy videos on YouTube raised concerns about informational value (Lo AS et al, Epilepsy Behav 2010, 17: 541). We reviewed 100 YouTube videos for content, informational accuracy, intent of posting, and to assess issues of individual privacy.

Methods: YouTube was accessed on 4/25/2010 and the top 50 video posts identified by searching “seizure” (31,700 hits), “epilepsy” (9.690 hits), and “convulsion” (1,090) were reviewed. 50 additional home videos were identified starting with the highest rated searching by “seizure” then serially following the highest recommended link. All videos were rated by consensus of an epileptologist, EEG technologist, and epilepsy nurse. The 100 final videos included 71 home videos, 2 videos from epilepsy monitoring unit admissions, 23 professional multimedia videos, and 4 cartoons.

Results: 34% were posted as humor/entertainment, 35% education, 30% requesting help, and 24% as part of a blog. 33% were labelled as showing seizure, but were deemed to show a non-epileptic event. The most widely viewed of all 100 were a television clip of a celebrity imitating a seizure (1,753,051 hits), a home video encouraging discontinuation of antiepileptic drugs in favor of medical marijuana (919,061 hits), and a cartoon of an individual faking a seizure to obtain narcotics in the emergency department (704,676 hits). The top 5 professionally made educational videos were viewed a mean of 126,353 times. The top 5 “humor” posts were viewed a median of 238,135 times. 20/100 showed someone faking a seizure as humor. 7 showed an epileptic seizure filmed by witnesses and posted as humor. In all home videos, subjects were easily visually identifiable and the majority included the subject’s name. Many included additional identifying information such as age or details of medical history. 51/71 (72%) home videos showed a pediatric patient, 32 posted by a parent. These had a mean of 30,018 hits. Expressed parental intent in posting these videos was requesting help (47%), to educate others (19%), blog content (28%), or unknown (6%).

Conclusions: YouTube is used a source for epilepsy education and information, however many videos - including the most popular - are stigmatizing or contain medical misinformation. Professional educational videos are less widely viewed than those portraying seizures as humorous. Home videos of children with epilepsy comprised half of the reviewed content, usually posted by a parent. Privacy issues are of concern, particularly for pediatric patients unable to personally consent to online posting of potentially sensitive videos, particularly as these are widely viewed.

2.332

INDETERMINATE EMU ADMISSIONS: DOES REPEATING THE ADMISSION HELP?

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Rationale: Inpatient video EEG monitoring is an important tool in spell classification and is currently the gold standard. The diagnostic yield of an Epilepsy Monitoring Unit (EMU) admission provides clinically important information in 60% to 72% of the admissions. The yield of subsequent EMU readmissions after an initial non-diagnostic first admission has not been well established. The objective of this study is to determine the diagnostic yield of repeat EMU admissions or subsequent ambulatory EEG for spell classification in patients who have had an indeterminate initial EMU admission.

Methods: A retrospective chart review and analysis was conducted consisting of all EMU admissions to the Mayo Clinic Hospital Arizona between January 2007 and December 2009. Admissions for spell classification were included. Admissions for presurgical evaluation, seizure quantification and medication adjustment were excluded. The cases with indeterminate diagnoses on first EMU admission were reviewed to determine if repeat EMU admission or subsequent ambulatory EEG lead to a diagnosis. Note was made of any therapeutic changes after an indeterminate initial evaluation.

Results: Total of 805 EMU admissions occurred between January 2007 and December 2009, of which 534 (66%) were for spell classification and diagnosis. 428 (80%) received a diagnosis after the first admission, leaving 106 (20%) where the diagnosis was indeterminate based on inability to record a typical event. Of the 106 indeterminate admissions, 13 (12%) went on to have a second admission. During the second admission, 8 (62%) were diagnosed. Four patients went on to have a third admission with none of them receiving a diagnosis. One patient had a fourth admission, again with no diagnosis. 19 (3%) patients had ambulatory EEG monitoring after an indeterminate admission with only one (5%) receiving a diagnosis after ambulatory EEG monitoring. Even in patients who were initially indeterminate, medication management changed 37% of the time.

Conclusions: Admission to the Epilepsy Monitoring unit was helpful for spell classification and diagnosis with 80% of the patients receiving a diagnosis after the first admission. The diagnostic yield after the second EMU admission was also high at 62%. Very few patients go on to have a 3rd and 4th admissions, with none of them receiving a diagnosis. Yield for ambulatory EEG monitoring for 24-72 hours was after an indeterminate EMU admission was low. However, even in cases where a definitive diagnosis was not reached, EMU admission was still helpful, as medication management was frequently changed. After an initial indeterminate admission, a repeat EMU admission should be considered. If no diagnosis is made after the second EMU admission, subsequent admissions are unlikely to produce a definitive diagnosis.

2.333

ASSESSING YOUTUBE VIDEOS AS A TEACHING TOOL FOR INFANTILE SPASMS

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Rationale: The educational value of videos in medicine is well established, in particular in Pediatric Neurology where integrated multimedia has proven to be highly effective in educating both patients and medical staff. Given the widespread practice and potential repercussions of using YouTube as a source of information, available videos on YouTube portraying infantile epileptic spasms were reviewed for their efficacy as a proper educational tool by assessing their quality and diagnostic veracity using a novel rating system.

Methods: The top 25 YouTube videos under each of the search terms “infantile spasms”, “spasms, “epileptic spasms” and “West syndrome” were reviewed in November 2009. A Medical Video Rating System (MVRS) was devised and all videos were reviewed and scored by a staff neurologist (primary rater) using this scale to assess quality and diagnostic veracity. Videos were considered relevant only when displaying clinical examples of infantile epileptic spasms. In the first component of MVRS, technical quality of the relevant videos was scored by assessing lighting, sound, angle, resolution and duration out of a total score of 5. The videos displaying the proper diagnosis were then rated as being excellent (5/5), good (4/5), fair (3/5), poor (4/5) or very poor (1/5) clinical examples of infantile spasms in the second component of the rating system. Inter-rater variability of MVRS was assessed by having a second staff neurologist (secondary rater) rate the videos. McNemar’s test was then used to determine whether the scores across the two raters were significantly different from each other.

Results: Of the 100 videos obtained across all four search terms, 50% were deemed to be irrelevant by both raters. While the term “infantile spasms” yielded 75% of relevant videos, the term “West syndrome” yielded only 25% of relevant videos. Of all relevant videos, 60% obtained a perfect technical score, 54% had the proper diagnosis of infantile spasm and 29% were judged to be excellent clinical examples as assessed by the primary rater. The Medical Video Rating System possesses good inter-rater concordance with only a 10% disagreement between the primary and secondary raters for all examples. The scores were not considered to be statistically different using McNemar’s test. Non-epileptic paroxysmal events wrongly labeled as infantile spasms included self gratification disorder, gastric reflux, dystonia and normal infant behavior.

Conclusions: There are readily available examples of infantile spasms posted on YouTube. From a technical perspective, the majority of videos meets adequacy but content relevance varies depending on the search term utilized and only a minority of videos(10%)are excellent clinical examples with a potential for being used in medical education. The proposed rating tool known as MVRS possesses good inter-rater agreement and can be used to assess the reliability of videos as a teaching resource in infantile spasms. Such a tool can potentially be applied to evaluate video resources in other paroxysmal events and movement disorders.

2.334

EPILEPSY AND ACTIVITY - A POPULATION BASED STUDY

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Rationale: To compare the activity profiles of a nationally representative sample of individuals with epilepsy compared to the general population.

Methods: The Canadian Community Health Survey is a cross-sectional survey that uses a stratified cluster sample design to obtain information on Canadians 12 years of age or older. Data on activity and energy expenditure, among those aged 12-39 years, were compared for those who reported having epilepsy and the remainder of the population.

Results: Of the 53,552 respondents, 341 reported having epilepsy. There was no difference in the monthly frequency of leisure physical activity of >15 minutes duration between those who did and did not have epilepsy. The daily energy expenditure related to leisure physical activity was also similar between the two groups. The choice of leisure activity was similar, but those with epilepsy were more likely to use walking as a leisure physical activity and were less likely to be involved in ice hockey, weight training, and home exercise.

Conclusions: These results suggest that the negative attitudes towards restricting access to physical activity do not appear to be adversely affecting the leisure activity of Canadian youth and young adults with epilepsy.

2.335

POPULATION-BASED PREVALENCE AND INCIDENCE OF EPILEPSY IN WASHINGTON, DC

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Rationale: Epilepsy affects almost 2% of the U.S. population, however few studies provide prevalence estimates for low-income and minority populations. Using a multi-mode data collection model, we sought to determine epilepsy prevalence estimates for subgroups in Washington, DC, a racially and socio-economically diverse community.

Methods: Probability-based sampling was used to select 20,000 DC addresses. Sample households were asked to complete a short screener by mail or web, and later by phone, regarding demographics and epilepsy status of each resident. Nonrespondents were contacted again and offered an increase in incentive to complete the screener. Respondents of all ages with a history of epilepsy were sent a questionnaire which asked about their seizures, treatment, and co-morbidities. Screener data were weighted using the March 2009 supplement of the Census Bureau's Current Population Survey to reflect the entire DC population of 581,847.

Results: 6,447 households representing 12,894 individuals (10,753 adults and 2,141 children) responded to the screener for a response rate of 35% after adjusting for undeliverable mail. Individuals were 39% White, 47% Black, 6% Hispanic, and 8% Other race/ethnicity. 208 (174 adults and 34 children) cases with a history of epilepsy were identified. Of these, 69% reported having a seizure disorder but not epilepsy. The overall weighted prevalence of epilepsy was 1.8%, active epilepsy was 0.9% and incidence of epilepsy was 64/100,000. Blacks had a higher prevalence (2.4%) than Whites (1.0%, $p<.001$) and a higher incidence (109/100,000) compared to Whites (34/100,000, $p<.001$). The incidence of epilepsy was bi-modal with the highest rate in children <3 years of age and a lower rate of new cases in the elderly. Adult residents living in DC for <3 years had a prevalence of 0.9% compared to 2.0% for those living in DC for >3 years. Prevalence was inversely related to education in both Blacks and Whites ($p<.0001$). Full questionnaires were obtained from 121 (58%) of the cases. 46% were currently taking an AED. Notable co-morbidities included depression (29%), attention problems (15%), memory problems (20%), stroke (10%), alcohol dependence (13%), anxiety (25%), and developmental impairment (12%). 29% of adult cases were unemployed or unable to work and 27% reported that seizures or epilepsy affected their ability to work or keep a job.

Conclusions: Epilepsy prevalence in Washington, DC varies significantly by race and education. Overall, residents with a history of seizures are unfamiliar with the word epilepsy even though almost half are currently taking a medication for their seizures. Adult residents that are more native to DC have a higher prevalence of epilepsy than those new to the city, suggesting a "healthy mover" effect. However, in this cross-sectional study we cannot conclude whether epilepsy discourages relocation or whether both are confounded by race, education, income, and/or access to health care. Similar to other studies, we found that people living with epilepsy in DC are significantly affected by co-morbidities related to brain function and by unemployment.

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PREDICTORS OF DEATH IN PEDIATRIC IN-PATIENTS WITH STATUS EPILEPTICUS

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Rationale: To evaluate in-patient mortality and predictors of death during status epilepticus (SE) in a large, nationwide, pediatric cohort.

Methods: We identified our cohort from the KIDS Inpatient Database for the years 1997-2006. We queried the database for SE, and for associated diagnoses as well as death while inpatient. Predictors of death were determined using logistic regression analysis.

Results: We identified 12,365 (5541 female) patients with SE among 14,965,571 pediatric inpatients (0.1%); of these 117 died while in the hospital (0.9%). Mean age was 6.2+/-5.5 years (range 0 to 20 years). The sample included 49% Caucasians, 21% Hispanics, 20% African Americans, as well as other ethnicities (9%). Most frequent admission ICD 9 code diagnoses in addition to SE were cerebral palsy, pneumonia, and respiratory failure.

None of the socioeconomic factors examined were significant risk factors for death. Independent risk factors for death in patients with SE included near drowning (Odds Ratio (OR) 43.2; Confidence Interval (CI) 4.4-426.8), hemorrhagic shock (OR 17.83; CI 6.5-49.1), sepsis (OR 10.14; CI 4.0-25.6), aspiration (OR 9.1; CI 1.8-47), mechanical ventilation > 96 hours (OR 9; CI 5.6-14.6), transfusion (OR 8.25; CI 4.3-15.8), structural brain lesion (OR 7.0; CI 3.1-16), hypoglycemia (OR 5.8; CI 1.75-19.2), liver failure (OR 14.4; CI 5-41.9), admission in December (OR 3.4; CI 1.6-4.1) and African American ethnicity (OR 0.4; CI 0.2-0.8). Area under the ROC curve for this model is 0.846.

Conclusions: Pediatric status epilepticus occurs in up to 0.1% of pediatric inpatient admission, with a mortality of up to 1%. There appear to be several co-morbidities and risk factors that can predict mortality. These may warrant additional monitoring and aggressive management of status epilepticus, and prospective studies to validate these observations.

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DIAGNOSIS AND HOSPITAL STAY FOR STATUS EPILEPTICUS: GENDER DIFFERENCES OVER A DECADE

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Rationale: Epilepsy is a common disorder with a prevalence of approximately 6.4 per 1,000 patients. A recent CDC study reported that up to 2.1% of Tennesseans might be affected by Epilepsy. Status epilepticus, a unique state of an epileptic seizure incapable of spontaneous resolution, is associated with high rates of morbidity and mortality. In this analysis, we examined the incidence of status epilepticus (as a primary diagnosis) by gender among adult patients hospitalized from 1997-2006 in the state of Tennessee, USA

Methods: We extracted relevant data on adults 18 years and older pertaining to ICD-9 code (345.3) for status epilepticus from Tennessee Hospital Discharge Data System (HDDS: 1997-2006). We reviewed the number of emergency visits for these patients as well as the duration of hospital stay. Hospitalization rate of these patients was age adjusted per 2000 census data.

Results: Age adjusted rates per 100K ranged from 0.7 - 4.0 per 100,000 for inpatient from 1997 to 2006 and for ED discharges, it Ranged from 0.01 to 0.1 per 100k. Total number of ED visits for status epilepticus increased significantly from 33 in 1997 to 87 in 2006, males were more likely to present themselves to ED for status epilepticus. Further, males presenting for ED services tripled from 16 cases in 1997 to 48 cases in 2006. Similarly inpatient discharges with a final diagnosis of status epilepticus were higher for males than females (83 in 1997 to 138 in 2006 for males vs. 84 in 1997 to 102 for females). Further, the duration of hospital stay was longer for females than males in 2006 (4.54 days for males vs. 6.36 days for females) suggesting that females had more complex and severe problems associated with status epilepticus, which required longer treatment.

Conclusions: The hospital-based prevalence for status epilepticus in TN appeared to have increased over time and it is higher for men than women. Hospital stay for men with status epilepticus has decreased compared to females, which indicates that severity of status epilepticus is higher among females requiring hospital longer treatment. Future research needs to focus on this gender health disparity and compliance with antiepileptic medications regarding status epilepticus among adults

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PREVALENCE OF SLEEP DISORDERS SYMPTOMS IN CHILDREN WITH EPILEPSY AND TYPE 1 DIABETES

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Rationale: Children with epilepsy have a higher rate of impaired sleep than normal children, including altered sleep architecture and reporting symptoms of disordered sleep. The aim of this study was to compare the prevalence of sleep disorder symptoms in children with epilepsy versus controls and another chronic condition, type 1 diabetes (DM), to ascertain specificity to epilepsy.

Methods: After obtaining IRB permission from Rush Medical Center and Stroger Hospital, the Pediatric Sleep Questionnaire was administered to parents of children 2-18 years old with epilepsy (n=71), normal children (n=52) and children with DM (n=25). Subjects were recruited from child neurology, pediatrics and endocrinology clinics. Between-group analyses were completed using chi-square tests to compare the frequency of symptoms on the questionnaire. Using the Bonferroni correction, significance was established if $p<0.001$.

Results: Patients with Epilepsy vs. Controls:

The mean age of patients with epilepsy was 9.7 years (SD=4.3) and was 7.1 years (SD=4.1) in controls. Children with epilepsy were significantly more likely to have difficulty with sleep ($p<0.001$). Symptoms of sleep-disordered breathing were more likely in children with epilepsy, including apnea (20% vs. 0%), shaking the child to get him to breathe and awakening with a snort (all $p<0.001$). Restless sleep, leg restlessness, brief kicks of the legs and repeated kicks of the legs (26% vs. 10%) were more likely in children with epilepsy (all $p<0.001$). Teeth grinding, but not other parasomnias, was seen more in the epilepsy group (50% vs. 27%; $p<0.001$). Bedtime rituals and routines were seen more frequently in children with epilepsy, as were awakening more than twice per night and trouble falling asleep after awakening (all $p<0.001$). Symptoms of daytime hypersomnolence were also more likely, including waking up unrefreshed (53% vs. 27%), feeling sleepy, an irresistible urge to nap (38% vs. 12%) and having a teacher say the child appears sleepy (45% vs. 6%) (all $p<0.001$). Parents of children with epilepsy were more likely to have trouble awakening their children (42% vs. 21%; $p<0.001$).

Patients with Epilepsy vs. Patients With DM:

The mean age of DM patients was 13.3 years (SD=4.0). All of the significant differences between patients with epilepsy and controls were maintained in comparing patients with epilepsy and DM (all $p<0.001$), with the exception of awakening unrefreshed and being hard to awaken in the morning. Additionally, patients with epilepsy were more likely than patients with DM to snore, breathe loudly and nap (all $p<0.001$).

Conclusions: This study suggests that patients with epilepsy are at an increased risk for daytime hypersomnolence and sleep disorders, including sleep-disordered breathing and periodic limb movements of sleep, compared to controls. It also suggests that these risks are not due to the burden of having a chronic condition alone. This is an important finding, as impaired sleep may decrease seizure threshold, perpetuating further seizures in children with epilepsy and prompting further workup and treatment of specific sleep disorders.

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PATIENTS WITH A LIFETIME OF EPILEPSY: CHARACTERISTICS AND CO-MORBIDITIES

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Rationale: New onset seizures in the elderly is well described. However, many patients with epilepsy grow old; the aim of this cross-sectional study is to more clearly define the impact on health and psychosocial functioning of a lifetime with epilepsy.

Methods: Thirty-nine patients were selected from a single community epilepsy practice. Inclusion criteria was age of >65 years, and at least a 30 year duration of epilepsy.

Results: The median age was 71 years (range 65 to 92). The median duration of the epilepsy was 51 years (range 27 to 84 years). Seventy-three percent of patients had partial epilepsy, 24% generalized epilepsy and 3% mixed generalized and partial epilepsy. Of the 24 patients with partial epilepsy, 10 had known causes including head truama (1), mesial temporal sclerosis (3), vascular malformation (3), encephalitis (1), meningioma (1) and birth hypoxic injury (1). Three patients had a history of status epilepticus. Five patients had falls with injuries including fractures, concussions, or back injury. The median longest seizure free period was 8 years (range 2 days to 40 years). Fifteen patients had periods of seizure freedom longer than 5 years. Assessing seizure control over time, 33% of patients were improved, 30% were unchanged, and 36% were worse.

Eighty-three percent of patients had been employed, with professions ranging from executive vice-presidents to nurses, teachers, and housewives. Two patients lost their profession due to seizures. Eighty percent were married, 10% unmarried, and 10% divorced. Thirty-two patients had children. The mean number of years of education was 13 years (+/- 4). Forty-two of patients were on one antiepileptic drug (AED), 37% on 2 AEDs, 13%on 3 AEDs, and 7% on 4 AEDs. One patient had a vagus nerve stimulator. The median number of lifetime AEDs was 4 (range 1 to 10)

35% of patients were still driving. 18% of patients had osteoporosis, and 18% had osteopenia. The incidence of major drug side effects was rare: one patient developed B cell lymphoma from carbamazepine and several patients had phenytoin associated rashes or gingival hypertrophy. No major side effects were seen with the newer AEDs. Six patients had a major depressive or anxiety disorder, and five patients were psychiatric medications. There was no history of suicide attempts.

Conclusions: Elderly patients with long-standing epilepsy were more likely to have relatively well controlled partial epilepsy. Many patients had long periods of seizure freedom during their lifetime. The incidence of major drug side-effects or co-morbidities was low, most commonly low bone density and depression. Most patients had professions and families despite their epilepsy. This study demonstrates that despite a long history of epilepsy, patients may reach old age without high risk of physical or psychosocial disability.

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A PROSPECTIVE STUDY OF A COHORT OF PATIENTS WITH NEWLY-DIAGNOSED EPILEPSY: THEIR RESPONSE TO MEDICATION, AND THE ROLE OF EEG AND MRI

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Rationale: Approximately 30% of patients with epilepsy have inadequate control of seizures with drug therapy. We present a cohort of patients with newly-diagnosed epilepsy and assess response to first, second and third adequate trials of antiepileptic drugs (AEDs), as well as the role of EEG and MRI in the development of intractability.

Methods: All patients seen in the new-onset seizure clinic at the London Health Sciences Center/University of Western Ontario-Epilepsy Programme, with newly-diagnosed epilepsy, were included in a prospective and systematic way since 2006. Demographics as well as clinical history were obtained. Epilepsy was classified as idiopathic, symptomatic, or cryptogenic. Response to treatment with antiepileptic medication was assessed. Patients were considered to be seizure-free if they had not had seizures of any type in between visits. Results of MRI and EGG were analyzed as well.

Results: 174 patients were included. The mean age was 37 years (range: 10-84). Information was available for 139 patients. Of these 83 (59.7%) became seizure free and 56 continued to have seizures. When the two groups were compared, there were no differences in sex, history of febrile seizures, and family history of seizures ($p > 0.05$). The median age of onset was 36.8 years in those who became seizure free, and 31.2 years for those who persisted in having seizures. Of the ones who did not become seizure free with the first AED trial, response to a second trial of AED was seen in 20 (14.3% of total). Only 1 (0.8%) person became seizure free after a third trial of AED. Mean follow up was 17.2 m (SD +/- 10.13m). The most common used AEDs were phenytoin (43), carbamazepine (38), and lamotrigine (29). As a second trial, lamotrigine was the most common used (24). Of those who became seizure free after the first trial of AED, 15 had normal EEG, and 28 normal MRI of the brain. Of the ones who did not become seizure free after 3 trials of AEDs, the EEG was normal in only 5 patients, and the MRI was normal in only 13.

Conclusions: Patients who began having seizures early in life and those with symptomatic epilepsy are likely not to become seizure free after treatment with the first AED. In general, response to first AED trial was seen in close to 60% of patients. EEG and MRI findings did not influence prognosis.

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PATTERNS OF HOSPITAL UTILIZATION AMONG PATIENTS WITH SEIZURES AND EPILEPSY

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Rationale: Visits to U.S. Emergency Departments (ED) by patients with seizures account for 1% of all ED visits or 1 million seizure visits annually (Pallin et al. 2008). Overall utilization of EDs in the United States is on the rise, showing a 14% increase between 1992 and 1999 (Cook at al. 2004, McCaig & Burt 1999). The aims of this study were to determine if differences and disparities exist across demographic characteristics, insurance status, and utilization between patients with and without epilepsy or seizure diagnoses using the Emergency Department in Yuma, Arizona.

Methods: Emergency Department (ED) data from YRMC between January 2005 to June 2008 were analyzed. Data on individual patients as well as patient visits were analyzed according to whether they had seizure (including epilepsy), epilepsy, or no seizure diagnostic codes in their visits, and whether the patients had ever been admitted to the ED for a seizure or epilepsy-related diagnosis (that is, had a seizure or epilepsy code as the principal diagnosis). Patients who had ever had a seizure diagnosis were coded as seizure patients, and patients who had ever had an epilepsy diagnosis were coded as epilepsy patients (they are also, by default, seizure patients).

Results: A total of 40,689 unduplicated patients presented to the YRMC ED from 2005-2008 for a total of 61,851 visits. A seizure diagnosis was present in 3% of all cases that came to the YRMC from 2005-2008, with seizures accounting for 1.74% of all ED visits. Epilepsy related visits accounted for 0.3% of all ED visits. Seizure patients had a high rate of repeat visits across multiple years; 42% of the seizure cohort had multiple yearly visits, the non-seizure cohort had only 15% visiting within two or more years. Seizure patients were 2.76 times more likely to have visits within 2 or more years compared

to non-seizure patients. Principal seizure patients had a higher rate of multi-year visits, 43.6% visiting the ED within 2 or more years. Epilepsy and seizure patients were significantly younger than the non-seizure and non-epilepsy cohorts.

Conclusions: Epilepsy and seizure patients had high utilization rates within each year and across the study period. Patients who had ever been admitted to the ED due to seizures or epilepsy had higher rates of utilization even if the subsequent admissions were not seizure-related. Insurance status was not a predictor of repeat ED usage by epilepsy patients.

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THE DIAGNOSIS OF NON-EPILEPTIC SEIZURES ON EEG TELEMETRY REDUCES ACUTE HEALTH CARE UTILIZATION

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Rationale: Non-epileptic attacks are common and account for 20-25% of all intractable seizure disorders referred to epilepsy centers. Most are found lacking organic cause and are presumed psychogenic in origin. Non-epileptic attacks are frequently suspected at a single clinical encounter, but the diagnosis is usually only made with certainty following prolonged video-EEG telemetry recording. Similar to epilepsy, these patients are disabled by their paroxysms, and they frequent Emergency Departments without clear diagnoses. The burden to both patients and the health care system is therefore considerable. This study aims to determine whether the diagnosis of non-epileptic seizures on video-EEG telemetry is effective in reducing the utilization of acute care health resources.

Methods: All patients undergoing EEG telemetry and discharged between January 1st 2002 and December 31st 2007 with a diagnosis of non-epileptic seizures were included in the study. The province-wide electronic health care record was used to establish patients' Emergency Department (ED) visits. Patients who had no history of ED visits either during the 24 months prior to, or the 24 months following the date of diagnosis were excluded from the study.

Results: Twenty-one cases were identified, 67% female, with mean age 44.4 years of age, and 19% had co-existent epilepsy. Average duration of EEG was 8.1 days and 6.1 non-epileptic events were recorded. ED visits were reduced during the 24 months following (3.73 +/- 3.78; mean +/- SD) compared to the 24 months preceding (5.55 +/-5.94) the diagnosis ($p<0.1$, Wilcoxon signed rank test). There was no difference in the number of psychiatric visits to the ED following the diagnostic admission.

Conclusions: The diagnosis of non-epileptic seizures by video-EEG telemetry is associated with a reduced rate of ED visitation during the two years following hospital admission. These findings suggest that telemetry not only helps relieve diagnostic uncertainties for the patient and physician, but also has quantifiable benefits for an over-extended and costly area of health care utilization.

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LACK OF RELIABILITY OF ICD9 CODES FOR GENERALIZED CONVULSIVE STATUS EPILEPTICUS DETECTION

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Rationale: The incidence and response to first line therapy of status epilepticus (SE) is known from prospective population based studies but there have been no prospective studies to determine the incidence of benzodiazepine refractory SE using contemporary dosing. Its incidence may be obtainable from retrospective case review, similar to other aspects of SE that have been reported. Many studies have retrospectively identified SE based on ICD9 codes. Thus, we performed a retrospective database review to determine whether retrospective SE case identification based on ICD9 codes is accurate for identifying cases of acute generalized convulsive SE (GCSE) and determined the incidence of identifiable GCSE.

Methods: We retrospectively reviewed the ICD9 coding database for visits to the University of Virginia Hospital, Charlottesville, Virginia from 1/1/2009-12/31/2009 for primary and secondary SE codes (345.2 "petit mal status", 345.3 "grand mal status", and 345.7 "epilepsia partialis continua") and reviewed the medical records of each case to determine if patients coded as SE met criteria of GCSE presenting to the University of Virginia Emergency Department (ED). SE was defined as seizing on ED arrival or greater than 3 seizures without return to baseline. We also reviewed the same database for visits with an epilepsy primary diagnosis code of 345.0-345.9, excluding SE codes; the medical record from every twentieth case was reviewed to determine if any visits for SE were miscoded using other seizure and epilepsy diagnosis codes.

Results: 145 visits were coded 345.2, 345.3, or 345.7 as primary or secondary diagnosis codes. Of the 115 coded 345.3, only 21 (18%) visits met our criteria for acute GCSE. If the criteria are expanded to include presentation of GCSE to an outside hospital ED but with clinical stabilization by the time of transfer to the UVA ED, then 31 visits (27%) met our criteria for acute GCSE. Of the 30 coded 345.2, none met our criteria for acute GCSE. No visits to the ED were coded 345.7.

Conclusions: Retrospective analysis of coding databases is not an accurate way to identify incidence of GCSE since a large majority of cases coded for status epilepticus do not meet criteria for a diagnosis of acute GCSE. Prospective studies or different methods of retrospective review are necessary to perform accurate case identification of SE in clinical research.

This retrospective review also suggests that the incidence of SE is low and many centers must be included in a treatment trial of benzodiazepine refractory SE.

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RACIAL/ETHNIC DIFFERENCES IN INCIDENT EPILEPSY/ SEIZURE DISORDER FOLLOWING ADMISSION TO US NURSING HOMES, 2003-2007

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Rationale: Seizures can follow certain precursor conditions, and the prevalences of those conditions differ by race/ethnicity. With the racial/ethnic makeup of US nursing home (NH) residents changing with the US population. NH caregivers and administration should understand racial/ethnic differences in precursors and subsequent seizures due to the potentially severe consequences that seizures hold for elderly residents. We hypothesize that, following each of several precursor conditions, incident epilepsy/seizure disorder (epi/sz) rates will differ by race/ethnicity among NH elderly.

Methods: We first examined Minimum Data Set (MDS) data for residents, age 65+ years with race/ethnicity available, at admission (N=3,585,969) to any Medicare/Medicaid certified US NH during 2003-2005 for indication of epi/sz. Epi/sz was MDS-derived as: ICD-9 code 349 or 780.39, sz as a current condition, or epilepsy-related mental retardation/developmental delay. Those with no such indication, and with e"1 follow-up MDS (N=2,775,299), were then followed through 2007 or end of NH stay for new-onset epi/sz.

Results: Of 2,775,299 NH admissions followed forward, 226,768 (8.2%) of admissions were Black non-Hispanic (B), 2,423,006 (87.3%) were White non-Hispanic (W), and 125,525 (4.5%) were Hispanic or other race (O). 63,818 (2.3%) had incident epi/sz, for a rate of 17.4 new cases per 1000 person-years (PY) of follow-up: 30.6/1000PY in B, 15.8/1000PY in W, 23.6/1000PY in O. Prevalence of stroke at admission was 26% (B), 17% (W), and 23% (O), with incident epi/sz among those with stroke of 48.5/1000PY (B), 28.8/1000PY (W), and 39.3/1000PY (O). Prevalence of hemiplegia at admission was 11% (B), 5% (W), and 10% (O), with incident epi/sz among those with hemiplegia of 56.9/1000PY (B), 39.3/1000PY (W), and 45.9/1000PY (O). Prevalence of hypertension at admission was 77% (B), 65% (W), and 70% (O), with incident epi/sz among those with hypertension of 31.0/1000PY (B), 15.8/1000PY (W), and 24.3/1000PY (O); similar differences were seen for those with diabetes, Alzheimer's disease, non-Alzheimer's dementia, and/or cancer at admission. All rates differed significantly by race/ethnicity, with the higher rates for O largely driven by higher Hispanic rates compared to Native American/Alaskan Native and to Asian/Pacific Islander. Incident epi/sz among those with none of these conditions at admission was 23.5/1000PY (B), 12.0/1000PY (W), and 14.7/1000PY (O).

Conclusions: For most of the precursor conditions examined, highest prevalences were seen among B and lowest among W. As hypothesized, incidence rates for epi/sz differed by race/ethnicity for all precursor conditions, with highest rates among B, lowest rates among W, and O rates in between and largely attributable to Hispanic rates. This finding has implications for NH-implemented prevention of, and monitoring for, incident seizures. Ongoing research is investigating incident epi/sz and its association with precursor and other clinical conditions, NH staffing and quality of care, and NH neighborhood US Census characteristics.

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ETIOLOGY OF EPILEPSY IN SOUTHEASTERN BRAZIL: A POPULATION-BASED MRI STUDY

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Rationale: Although the prevalence of epilepsy is similar around the globe, the leading causes of epilepsy may be different from regions due to exposure to the risk factors such as infectious parasitic diseases. The objective of this study is to look for brain lesions in an incident cohort of patients with epilepsy.

Methods: This is a cross-sectional study undertaken in a catchment area of Campinas, a city with 1.1 million inhabitants in Southeastern Brazil. The study was carried out at the district of Barão Geraldo, with approximately 44.000 inhabitants using a dataset from a epidemiological survey in the same area as part of Demonstration Project of Global Campaign Against Epilepsy WHO/ILAE/IBE. We attempted to contact all the 174 individuals with age equal or above 13 years old and a confirmed diagnosis of epilepsy from the dataset. We were able to contact 139 patients, and 86 agreed to undergo MRI scan. The MR images were acquired in a 2T system (Elscint, Prestige, Haifa, Israel). The diagnostic protocol included coronal 3mm thick slice T1, T2 and proton density along the hippocampal axis; axial T1 and FLAIR sequences. We also acquired volumetric T1 isotropic voxel for multiplanar and curvilinear reconstruction. We did not use contrast agent.

Results: Sixty-nine (36 women) of 86 MRI exams were of good quality and available for analysis. Sixteen (23%) had normal MRI. Hippocampal atrophy was observed in 39 (56%) patients: three in the context of dual pathology (cavernoma, heterotopia, cortical displasia), two as part of hemispheric lesions, 15 (22%) associated with other cortical atrophy and/or subcortical lesions suggestive of microangiopathy, and remaining 19 had isolated signs of hippocampal sclerosis. Signs of microangiopathy and stroke were observed in nine patients (13%). Cortical developmental malformation was observed in two cases. Two had diffuse brain atrophy and one had signs of gliosis and surgical intervention. Signs suggestive of neurocisticercosis were observed in four patients with hippocampal atrophy.

Conclusions: Hippocampal sclerosis is the leading epileptogenic lesion in the general population of a developing country. The frequency of microvascular lesions appears high, which suggests that risk factors for stroke are neglected in patients with epilepsy.

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EPILEPSY-RELATED MORTALITY IS LOW IN CHILDREN: A 25 YEAR POPULATION-BASED STUDY IN ROCHESTER, MN

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Rationale: Mortality in pediatric epilepsy is up to nine times higher than the general population. Causes of death may be related to seizures (aspiration, status epilepticus, accidents or sudden unexplained death in epilepsy (SUDEP)) or due to an underlying neurodevelopmental disability (aspiration pneumonia, infection). Children with neurologic impairment and those with poorly controlled seizures are at highest risk. We previously reported mortality in a 10 year population-based cohort that was 0.79 per 1000 person years, lower than other studies. The aim of this study is to expand the population-based cohort to 25 years to determine the mortality rate, cause of death, and risk factors for mortality in children with epilepsy.

Methods: The Medical Diagnostic Index of the Rochester Epidemiology Project was searched for all children diagnosed with epilepsy while residents of Olmsted County from 1980-2004. These records were reviewed to last follow-up to determine the proportion of children who died, as well as the cause of death. In addition, all charts were reviewed to determine the age of onset of epilepsy, the number of anti-seizure medications (AEDs) used, seizure control, epilepsy syndrome, and the presence and severity of neurologic impairment.

Results: There were 12 deaths among 356 children diagnosed with epilepsy while residents of Olmsted County from 1980-2004, with a follow-up of 4366.4 person-years. While the overall mortality was 2.75 per 1000 person-years, the epilepsy-related mortality was only 0.46 per 1000 person-years. One child died of probable SUDEP, and the

second as a result of aspiration during a seizure. The other children died of respiratory complications of their underlying neurologic impairment (N=8) or from progressive neurometabolic/neurodegenerative disease (N=2). Significant risk factors for death included cognitive impairment, abnormal neurologic exam, frequent seizures, intractable epilepsy, and symptomatic epilepsy ($p<0.001$). No child with normal cognition and neurologic exam died.

Conclusions: In our population-based study, mortality in children with epilepsy was low, 2.75 per 1000 person-years. This is similar to reported population-based studies, but is 90 times higher than the previously reported mortality rates for the general pediatric population. Only 2 children died of seizure-related causes, while the others died of complications of their underlying neurologic disease. Although mortality in children with epilepsy is higher than the general population, this is mostly related to underlying neurodevelopmental disability, rather than epilepsy.

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WAIT TIME FOR FIRST MEDICAL ASSESSMENT AFTER A SINGLE UNPROVOKED SEIZURE, DOES IT MATTER ?

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Rationale: There is minimal epidemiologic data on the time needed to complete a medical assessment after a single unprovoked seizure. In this study we describe the waiting times for initial assessment, completion of investigations, final conclusions, outcomes and safety in 51 single unprovoked seizure patients in a Canadian neurological referral clinic

Methods: We performed a retrospective chart review. Data was collected from January 2007 to March 2010 on all patients referred to the regional epileptologist. We identified 51 patients fulfilling the criteria for a single unprovoked seizure

Results: Median age at single seizure was 40 years (range 17-84). Median waiting times to see epileptologist from date of single seizure was one month (range 0 to 223, mean 15.18 months), 54.9% of patients seen within 2 months. The median wait time for EEG was 2 months (0 - 226, mean 14.34 months), 59.6% of the EEGs were performed within 2 months. Mean wait time for CT-head scan was 11.11 (-10 to 225) months, 55% of these were performed within 48 hours of event. Median waiting time for brain MR-imaging was 5 (0 -102, mean of 13) months; 59.3% within 6 months. The initial assessment was performed in 42.6% by ER physician, 25.9% by family physician, 7.4% by internist, 14.8% by neurologist and 3.7 by unknown physician. The diagnosis of seizure disorder by epileptologist differed only by 9% from original assessment. Anti-epileptic medication was initiated in 20.4% of patients prior to referral. Most frequently used AEDs were phenytoin (33%) and lamotrigine (27.8%). The decision to treat was attributed to seizure recurrence in 16.7%, EEG abnormalities in 18.5%, 13% due to imaging findings, and other reasons in 51.8%. Seizure recurrence was 25.5% (n=13) and was associated with imaging-abnormalities in 46.2%, and EEG-abnormalities in 38.5%. During the waiting period, minor injuries were reported in two patients, but no reported mortalities. Driving restrictions were verifiably recommended in only 3% of patients by primary care physician

Conclusions: This study showed referrals and assessment of single unprovoked seizure patients is being carried out in a reasonable time and was safe with no case fatalities. Although there were no major complications in patients, some of them waited more than one year to be assessed. Further improvement needs to be done with regards to obtaining earlier imaging (CT/MRI). Education of primary care physicians is important to avoid unnecessary delays and mismanagement of patients

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ATTITUDES RELATING TO DRIVING AND RISK TAKING IN ADOLESCENTS AND YOUNG ADULTS WITH EPILEPSY

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Rationale: There is no study in the literature that discusses attitudes towards driving and risk taking behaviour in adolescents and young adults. Given the importance of driving to and the prevalence of risk taking behaviours in this population, we compare attitudes towards driving and risk taking behaviour between adolescents and young adults with epilepsy and controls without chronic medical conditions.

Methods: This study collected data through a 'Teenager/Adolescent/ Young Adult Driving Questionnaire' and a 'Parental/Caregiver Questionnaire' designed by the authors. 55 adolescents/young adults with epilepsy completed the former questionnaire in pediatric neurology clinic or by mail, as did 102 otherwise healthy controls (i.e. no chronic medical conditions) obtained from orthopaedic clinic and from the pediatric emergency room. 55 parents of adolescents/young adults with epilepsy completed the later questionnaire, as did 54 parents of controls. Adolescents/young adults with epilepsy and controls were compared on questions like self-worth, judgement, drinking/drug use and motivations/perceptions/ concerns about driving.

Results: The mean age of the epilepsy and control groups were 17.6 and 18.1 years respectively, with no significant difference between male:female distribution. 60% of the epilepsy group did not know the type of epilepsy with which they were diagnosed, and neither did 50.9% of parents of the epilepsy group. Whereas 52.0% of controls had a drivers licence, only 27.6% of the epilepsy group did ($p=0.003$). Both the epilepsy and control groups had the same motivations for driving. Both groups felt that they have good judgment, believed that they could resist peer pressure and recognized that driving while drunk or high is always dangerous and illegal. Controls felt better about themselves than those in the epilepsy group (92.2% vs. 81.0%, $p=0.005$). 45.1% of controls admitted to getting drunk within the past year, compared to 27.6% in the epilepsy group ($p=.029$). The epilepsy group and their parents both believed that adolescents and young adults with epilepsy understand how to manage their epilepsy and would not make less safe drivers than most people. However, parents of the epilepsy group worried/had more concerns about their children's ability to drive a car, compared to parents of controls (27.3% vs. 7.4%, $p=0.024$).

Conclusions: This is the first study exploring attitudes towards risk taking and driving in this population, with some interesting findings. Adolescents and young adults with epilepsy often do not know their specific epilepsy diagnosis. They have the same motivations for driving as do their otherwise healthy peers, and similarly believe that they have good judgment and can resist peer pressure. Though fewer get drunk compared to their peers, the percentage that admit to this is worrisome given the relationship between alcohol and seizures. They have similar rates of illegal drug and marijuana use compared to their peers. Their parents have confidence in their judgment and ability to manage epilepsy, but have more reservations about their children's ability to drive.

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PREVALENCE OF EPILEPSY IN KOREA: NATIONWIDE STUDY FROM THE NATIONAL HEALTH INSURANCE STATISTICS

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Rationale: There has been no population based epidemiologic data for epilepsy of Korean. Our government-run medical security system that covers all the people and medical facilities enables nationwide epidemiologic study. We purposed to estimate the prevalence of epilepsy in Korean population.

Methods: We used database of Korean Health Insurance Review and Assessment Service and Korean National Health Insurance Cooperation. We identified epilepsy patients by anticonvulsant usage and proper diagnostic codes based on medical insurance claim. We analyzed the one year prevalence of each age group, gender, economic status and region, the pattern of anticonvulsant medication, and the medical cost for 2007.

Results: Overall prevalence of the patients who took anticonvulsant medication because of epilepsy was 2.41/1000. Age specific prevalence was lowest in 30s and 40s. In all age groups, the prevalence was higher in male than in female. Epilepsy was four times more prevalent in low income persons who receive medical aid. The prevalence was highest in Jeju island and lowest in Ulsan metropolitan city. In younger generation, new anticonvulsant was more frequently used. Total annual cost reaches 0.46% of total medical expenditure and 0.27% of total expenditure on health.

Conclusions: The overall prevalence of epilepsy in Korea is comparable those from contemporary studies performed in developed country. The prevalence is influenced by demographics, economic state and geography.

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SEIZURE REMISSION AND RELAPSE IN ADULTS WITH INTRACTABLE EPILEPSY: AN EXTENDED FOLLOW-UP STUDY

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Rationale: To investigate the cumulative probability of at least one year of seizure remission among adult patients with medically intractable epilepsy, and to determine the probability of subsequent seizure relapse among those who achieved remission.

Methods: A prevalence cohort of intractable adult epilepsy patients was identified from retrospective chart review of all patients seen in 2001 at the Columbia Comprehensive Epilepsy Center. Patients were included if they failed 2 adequate trials of antiepileptic medication and had more than one seizure per month for 3 months prior to an index visit in 2001. Outcome at a mean follow-up duration of 3.9 years was previously reported. The current study takes advantage of additional follow-up since our first study. Cumulative probabilities of seizure remission and subsequent seizure relapse were estimated using Kaplan-Meier analysis. Patients who underwent epilepsy surgery during follow-up were censored at the time of surgery. Cox proportional hazards models were used to assess the association between clinical factors and seizure remission as well as between clinical factors and seizure relapse.

Results: One hundred eighty seven subjects with intractable epilepsy were identified from 1308 patients screened. At the index visit in 2001, subjects had mean age of 41 years and mean epilepsy duration 25.6 years. Mean follow-up was 5.9 (SD ±2.4) years. At 8 years of follow-up the cumulative probability of seizure remission for more than one year was 22%, with estimated probability of remission about 3-4% per year. For most subjects, seizure remission was temporary, as 80% of subjects with remission relapsed by 5 years of follow-up. None of the clinical factors (history of status epilepticus, age of onset, developmental delay, etiology of epilepsy, mesial temporal sclerosis, history of febrile seizures, duration of epilepsy, number of failed AEDs, or history of epilepsy surgery) predicted the likelihood of achieving greater than one year seizure remission or subsequent seizure relapse.

Conclusions: Although some patients with intractable epilepsy achieve more than one year of seizure remission during medical treatment, most of these patients eventually have seizure relapse. No clinical predictors of remission or subsequent relapse were identified. These results provide further support that medical management alone is unlikely to render patients who have previously failed 2 AEDs seizure-free in the long-term.

IMAGE: images/878649_A.jpg

Kaplan-Meier estimate of cumulative probability of seizure remission lasting 12 months or more among 187 adults with intractable epilepy managed medically.

IMAGE: images/878649_B.jpg

Kaplan-Meier estimate of cumulative probability for subsequent seizure relapse among the 25 subjects who achieved seizure remission for 12 months or more.

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MORTALITY FOLLOWING CHILDHOOD STATUS EPILEPTICUS: A POPULATION-BASED STUDY

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Rationale: Hospital-based studies report increased long-term morbidity and mortality following childhood convulsive status epilepticus (CSE), but there is limited population-based data on the outcomes of CSE. Our group carried out the first prospective pediatric population-based study on CSE, the north London convulsive status epilepticus in childhood surveillance study (NLSTEPSS). Our current study aims to examine the medical, cognitive and behavioural outcomes, 5-10 years after an episode of CSE and in this report, we present preliminary mortality data.

Methods: From NLSTEPSS we have detailed contemporaneous sociodemographic and clinical data on all cohort members. In the current study, 219 cohort members who survived beyond 30 days of their CSE

were identified using unique patient identification numbers. Survival status was determined from hospital and national databases. In the deceased children, clinical details on cause of death were obtained from hospital records.

Results: 170 (77%) have been enrolled. Median age at CSE was 3.6 years (range 0.17-16) and median follow-up was 7.1 years (range 0.1-8). Thirteen children have died (0.08, 95% CI 0.05-0.13). The median age at death was 8.5 years (range 1.1-16.8). The etiology of CSE was remote symptomatic in 11 and cryptogenic in 2. The mortality rate was 1/100 person-years (95% CI 0.5-1.7) overall, and 2.3/100 person-years (95% CI 1.4-3.8) for remote symptomatic CSE. Most deaths were attributed to complication of the underlying etiology of CSE. Seven died as a result of aspiration pneumonia; one each had intestinal perforation, refractory status epilepticus and probable sudden unexpected death in epilepsy; and the causes of death are yet to be confirmed in three.

Conclusions: A substantial proportion of children will die within 5-10 years following CSE, with underlying aetiology of CSE being the most important determinant.

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SOCIO-OCCUPATIONAL AND EMPLOYMENT PROFILE OF PATIENTS WITH EPILEPSY

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Rationale: Epilepsy is a common neurological disorder that has a significant impact on quality of life. Many studies have observed higher unemployment rates among patients with epilepsy. However, unemployment rates vary according to the clinical conditions, country and group studied.

Methods: We performed a cross-sectional multicenter epidemiological study to evaluate the socio-occupational and employment profile of 872 adult patients with epilepsy followed in outpatient epilepsy clinics in Spain. The following characteristics and variables were analyzed: socio-demographic and clinical characteristics of the patients, socio-occupational profile in relation to different clinical situations and statistical association between the clinical variables and the socio-occupational situation of the patients.

Results: Between October 2007 and February 2008 872 questionnaires from patients with epilepsy were compiled by 82 neurologists. The mean age was 38.2 years (range 18-65). Focal epilepsy was present in 61.7% of the patients, generalized epilepsy in 35.3% and 3% had indeterminate epilepsy. Approximately one-fourth (27.7%) were refractory. Overall, 58% of the patients were active at the time of the survey, 10.9% of the patients were unemployed and 12.5% presented occupational incapacity. These data were similar to those of the general population in Spain in the first quarter of 2008, although unemployment rates were slightly higher among epilepsy patients than in general population (9.63%). Refractory epilepsy, having at least one seizure in the last 12 months, and polytherapy showed statistical correlation with an increased risk of unemployment. An increased risk of occupation incapacity was associated with patient age at disease onset before 10 years of age, presence of focal seizures, refractory epilepsy, at least one seizure in the last 12 months, and polytherapy.

Conclusions: Patients with epilepsy in Spain showed during the period from October 2007 to February 2008 employment rates similar to those of the general population, and slightly higher levels of unemployment. Some studies in other countries have reported higher unemployment rates in patients with epilepsy compared with general population. Differences between studies could be related to differences in cultural, social, political and economical differences between countries. The main factors associated with unemployment and incapacity were the presence of refractory epilepsy, the occurrence of a seizure in the last 12 months, and polytherapy.

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HOW OFTEN IS CHILDHOOD EPILEPSY “PREVENTABLE”?

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Rationale: Inadequate prenatal and obstetrical care, infection, and head trauma are risk factors for symptomatic childhood epilepsy worldwide. Low-income countries are most affected due to poverty, poor access to health care and social instability. Few studies have characterized recent incidence and outcome of preventable causes of childhood epilepsy in a resource-rich population. Our objective is to describe the incidence and types of preventable causes for childhood epilepsy in Olmsted County, Minnesota, a predominantly middle-class region with low unemployment and good access to high-quality medical care through either the Mayo Clinic, Olmsted Medical Center or a small number of private care practitioners.

Methods: This retrospective incidence cohort study include all residents d”18 years newly diagnosed with epilepsy (n=356) while living in Olmsted County between 1980 and 2004. We assigned one primary preventable condition per case to avoid double-counting cases with multiple conditions. Preventable causes were determined by consensus and based on available prevention methods such as quality obstetrical and perinatal care, childhood immunizations, mandatory seatbelt and helmet legislation, and access to tertiary care. Preventable causes were classified as prenatal, perinatal, and postnatal. Medically refractory epilepsy was identified in patients with seizures every 6-12 months despite adequate trial of two or more anticonvulsants.

Results: Overall, 56 of 356 patients had a preventable cause for their epilepsy (16% of all childhood epilepsy, male = 57%). Attributable etiologies were prenatal in 3 patients (5%), perinatal in 34 patients (61%), and postnatal in 19 patients (34%). The leading single preventable cause was premature birth d”37 weeks in 17 patients (30%), including 10 patients born between 33 and 37 weeks, who all had early abnormal neurologic examination or brain imaging. Other perinatal causes included hypoxic ischemic encephalopathy in 15 patients (27%), perinatal hypoglycemia in 1 patient, and neonatal stroke in 1 patient. Prenatal causes included congenital CMV (n=1), porencephalic cyst (n=1), and maternal respiratory failure due asthma (n=1). Epilepsy in previously healthy children occurred in 8 patients (14%) due to infectious etiologies (including 1 case of cerebral malaria), 4 patients (7%) after head trauma, 3 patients after hypoxic injury, 3 patients with childhood stroke, and 1 patient due to hypoglycemia. With an overall mean duration of follow-up 12.0 ± 1.0 years, medically refractory epilepsy was seen in 9 patients (16%) at 1-year after

epilepsy diagnosis, in 12 patients (21%) at 2-years after diagnosis, and 14 patients (25%) at last follow-up.

Conclusions: Despite advances in obstetrics and neonatal care, perinatal etiologies account for nearly two thirds of preventable causes of childhood epilepsy in a resource-rich population. A quarter of these children are at risk for medically intractable epilepsy, warranting continued efforts in possible methods of primary prevention.

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DEVELOPMENT AND VALIDATION OF A CASE DEFINITION FOR EPILEPSY FOR USE WITH ADMINISTRATIVE DATA

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Rationale: Administrative ICD-9 and ICD-10 data have been used in Canada for surveillance of chronic conditions such as diabetes. We have previously validated epilepsy ICD-9 and ICD-10 coding from inpatient and emergency visit databases in a large Canadian region. However, a majority of epilepsy patients are managed in outpatient clinics. We therefore conducted this study to: (1) Develop and validate coding algorithms for epilepsy using inpatient and physician claims data (captures both inpatient and outpatient visits); and (2) Assess whether adding an emergency room (ER) database to the inpatient and physician claims databases enhances the epilepsy case validity.

Methods: 720/2049 charts (35% of all visits) from 2003 and 1533/3252 visits (47% of all visits) from 2006 were randomly selected for review from 13 neurologists' practices as the "gold standard" for diagnosis. Epilepsy status in each chart was determined by 2 trained physicians with epilepsy management expertise. The optimal algorithm to identify epilepsy cases was then developed by linking the reviewed charts with the following administrative databases (ICD-9 and ICD-10 data from 2000-2008): a provincial health care insurance plan registry, a hospital discharge abstract database, an ER visits database, and a physician claims database in a large Canadian health region (Calgary). Accepting chart review data as the gold standard, we calculated sensitivity (Sn), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) for each ICD-9 and ICD-10 administrative data algorithm (case definitions).

Results: Of 2253 charts reviewed, 52% and 48% of charts were from epilepsy and neurology clinics respectively. 44% of charts reviewed represented epilepsy cases, 1% convulsion and 55% other diagnoses. The most commonly coded ICD-9 diagnoses based on chart review were 345.4 (localization-related epilepsy and epilepsy syndromes with complex partial seizures = 22%) and 345.1 (generalized convulsive epilepsy = 14%). Of 18 algorithms assessed, the best coding algorithm to identify epilepsy cases was 2 physician claims in 2 years or 1 hospitalization coded with an ICD-9 or ICD-10 epilepsy code (345 and G40/G41, respectively): (1) algorithm tested in 2002-2004: Sn 88.9%, Sp 92.4%, PPV 89.2%, NPV 92.2%; (2) algorithm tested in 2005-2007: Sn 93.1%, Sp 93.0%, PPV 91.9%, NPV 94.0%. Adding the ER database resulted in improved Sn and NPV but with lower Sp and PPV: (1) 2002-2004: Sn 95.6%, Sp 87.4%, PPV 84.3%, NPV 96.6%; (2) 2005-2007: Sn 99.3%, Sp 84.2%, PPV 84.3%, NPV 99.3%.

Conclusions: A majority of epilepsy cases can be accurately identified in administrative data using the following case definition: "2 physician claims within 2 years or 1 hospitalization (discharge abstract record)" coded with the epilepsy ICD-9 code 345 or ICD-10 codes G40 or G41. Validity of administrative data in recording epilepsy improved over time.

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EPILEPSY-RELATED DEATH IN ARIZONA: MAPPING RACIAL AND ETHNIC DISPARITIES IN MORTALITY AT COUNTY LEVEL

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Rationale: People with epilepsy have a high risk of premature death. Racial/ethnic disparities exist in the points of care and outcomes associated with epilepsy. Socioeconomic factors and not biological/ genetic differences appear to be mostly responsible for the ethnic/racial disparities in the outcome of epilepsy. The goal of Healthy People 2010 is to eliminate health disparities, including differences that occur by gender, race or ethnicity, education or geographic location. The first step towards eliminating racial/ethnic disparities in health is to identify high risk population and causes of disparities. The primary aim of this study is to identify statewide differences in epilepsy related mortality and correlate with ethnic/racial disparities. This may help with resource allocation towards potentially avoidable epilepsy related deaths.

Methods: The target population for the study comprised individuals who had died from an epilepsy-related death, in the state of Arizona, between 2007 and 2009. Data were collected from Arizona Vital Statistics, Department of Health Services. Statistical analysis was done with SPSS 18.0. Geo-epidemiological mapping was performed to highlight differences in mortality at county level. The state of Arizona comprises of 15 counties.

Results: During the 3 year study period, there were 176 deaths reported with epilepsy/status epilepticus as the immediate or underlying cause of death. Among the 176 deaths 97(57%) were female. The racial breakdown consists of: 116 (65%) non-Hispanic whites, 39 (22%) Hispanics/Latinos, 11(6.2%) American Indians, 6 (3.4%) African Americans, and 4 (2.3%) Asians/ Pacific inlanders . The mean age at death was 54 years (SD =25.82) and it varied between counties with minimum of 24 years (SD=20.6) (Mohave County) and maximum of 73 years (SD=2.83) (Apache County). Racial/ethnic disparity in mean age of death was noted among Hispanics (Mean=40 years, SD = 19.23); non Hispanic whites (Mean= 55 years, SD = 25.46) and American Indians (Mean= 49 years,SD =27.54). The proportionate mortality rate of epilepsy in the state of Arizona in 2007-2008 was 0.123% (parts of the 2009 data required for the PMR calculation were not available). Assuming the prevalence of epilepsy as 5 per 1,000; the calculated mortality rate was 2.06 per 1,000 patient-years. Causes of epilepsy related deaths were: status epilepticus (N=80;45%); SUDEP (N=5; 3%); direct epilepsy related (N= 6; 3.5%); accidents as a consequence of seizures (N=13; 8%) and suicide (N=2; 1%). Drowning was reported in 3 patients; thermal injuries in 2 patients and motor vehicle accident in 3 patients. Among the 176 deaths 8 (4.5%) were residing at the reservation and 22 (12.5%) were military veterans. Compared to Whites, the Hispanics had higher prevalence of cardiovascular disease.

Conclusions: Racial/ethnic disparity in mortality among epileptic patients is present in different counties of Arizona. Mean age at death among Hispanics and American Indians is younger compared to non-

Hispanic whites. This study identifies counties with maximum racial/ethnic disparity in mortality.

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ELECTROCARDIOGRAPHIC AND OXIMETRIC CHANGES IN PATIENTS DURING PARTIAL COMPLEX AND GENERALIZED SEIZURES

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Rationale: Significant autonomic changes occur during seizures and may be related to sudden unexplained death in epilepsy (SUDEP). Accordingly, we performed a study to determine the prevalence and spectrum of electrocardiographic (including heart rate and QTc) and oximetric changes during seizures in children and adults.

Methods: Patients admitted to our Epilepsy Monitoring Units were recruited prospectively to undergo quantitative analysis of ECG and pulse oximetry recordings obtained during seizures.

Results: 218 seizures from 76 patients were analyzed. Ictal sinus tachycardia occurred in 76% of patients (57% of seizures) and was associated with normal pre-admission MRI (23/25 with normal imaging versus 34/48 with abnormal imaging, Pearson's chi-square p=0.04), higher number of failed anti-epileptic drugs (6.1 +/- 3.0 drugs versus 4.4 +/- 2.5 drugs, independent-samples student's t-test 2 tailed p=0.025), and generalized seizures (58/79 generalized versus 66/138 complex partial, Pearson's chi-square p<0.001). Ictal sinus bradycardia occurred in 5.3% of patients (1.8% of seizures) and was associated with current beta blocker use (1/3 on beta blockers versus 3/73 off such medications, Pearson's chi-square p=0.026). Ictal hypoxemia occurred in 35% of patients (25% of seizures) and was associated with longer seizure duration (173 +/- 162 seconds versus 101 +/- 196 seconds, independent-samples student's t-test 2 tailed p=0.049), ictal tachycardia (17/34 with tachycardia versus 1/16 without, Pearson's chi-square p=0.003), and normal preadmission brain MRI (11/18 with normal imaging versus 7/31 with abnormal imaging, Pearson's chi-square p=0.01). Ictal QT prolongation (QTc > 30 ms) occurred in 45% of seizures, and was associated with ictal tachycardia (24/34 with tachycardia versus 3/9 without, Pearson's chi-square p=0.04) and temporal lobe onset (33/61 temporal versus 9/29 extratemporal, Pearson's chi-square p=0.04). Ictal attenuation of the QTc by > 30 ms occurred in 26% of seizures and was associated with generalized seizures (14/33 generalized versus 13/72 partial complex, Pearson's chi-square p=0.008) and obstructive sleep apnea history (3/3 with OSA versus 16/40 without, Pearson's chi-square p=0.044).

Conclusions: Ictal tachycardia and hypoxemia were associated with several known SUDEP risk factors including generalized seizure type, larger number of failed anti-epileptic drugs, prolonged seizure duration and normal neuroimaging. Ictal QT prolongation was more common than QT shortening, and was associated with ictal tachycardia. These findings may have implications for understanding the pathogenesis of SUDEP.

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EPILEPSY PARTNERSHIPS THAT WORK: THE SOUTH TEXAS BORDER— RIO GRANDE VALLEY REGION

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Rationale: A partnership with a non-governmental organization such as the non-profit, Epilepsy Foundation Central & South Texas (EFCST) and a governmental organization such as the Univ of TX Health Science Center's Dept of Neurology South TX Comprehensive Epilepsy Center (STCEC) has mutually beneficial results for both entities. For the STCEC, collaboration may result in direct applicability of new research approaches as well as collaboration with a grassroots organization that has relationships with epilepsy communities in Central and South TX. For the purpose of this presentation, grassroots is defined as an organization reflecting the voices and needs of the people served and which is largely led by these constituencies. Grassroots entities are responsive to the community because of their ability to integrate into the community, developing an emic perspective for best practices. In turn, collaboration with the experts at the STCEC inspires innovations and new developments for EFCST, and provides access to medical expertise. The connection to new knowledge, expertise, research, and developments are invaluable to EFCST. This partnership maintains working relationships with two important epilepsy community organizations, as well as capitalizes on collaborations that have facilitated serving a hard-to-reach population such as the South TX Rio Grande Valley Region (RGV).

A primary collaborative effort between both organizations is operating a mobile epilepsy clinic. EFCST in collaboration with STCEC provides services to 1,230 patients per year at the South TX Border - Rio Grande Valley clinics. In the RGV area the population is 89% Hispanic of which 82% primary language is Spanish. Of the population of over 900,000, almost forty percent live in poverty. The clinic patients are 95% Hispanic and primarily monolingual in Spanish. The majority of the clinic patients (90%) are uninsured. During a 9 month period this partnership provided 428 diagnostic laboratory tests and referred 20 candidates to STCEC for surgery. In addition 238 patients were enrolled in medication assistance programs and 2000 patients were referred for other services. The approximate monthly savings for all clinic patients is estimated at $49,471.89.

Methods: Building on this partnership, a proposed collaborative research effort will test programmatic and educational solutions to mental health disparities among Hispanics with epilepsy in the RGV area.

Results: A psychiatric comorbid condition that often occurs with epilepsy is depression, as well as other serious mental health conditions (Zeber, Copeland, Aumuan, Cramer, & Pugh, 2007). In the "Valley" this susceptibility is compounded by the need for linguistically and culturally appropriate services and bridging the many barriers to care.

Conclusions: The collaboration between EFCST and STCEC facilitates integrating health strategies to address the needs of patients based on empirical research and best practices. This presentation will provide an overview of the on-going research and the systemic processes of the partnership resulting in mutual benefit to the partners and patients.

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RESULTS OF A RANDOMIZED CONTROLLED TRIAL EVALUATING WEBEASE, AN ONLINE SELF-MANAGEMENT PROGRAM

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Rationale: WebEase (Epilepsy Awareness, Support and Education) is an on-line epilepsy self-management program designed to assist people with medication taking, managing stress, and improving quality of sleep. WebEase is based on social cognitive theory, the transtheoretical model and motivational interviewing, and consists of several components including a database to record personal information, three learning modules, a discussion board, fact sheets, and daily polls/quizzes. The aims of the study were to determine if older adolescents and adults who participate in the WebEase program show improvements in epilepsy-related knowledge, self-efficacy, medication adherence, stress management, sleep time and quality. The study also elicited user evaluation and input regarding the content and the format of the online program.

Methods: Adults ages 18 and older diagnosed with epilepsy, taking at least one anti-epileptic drug for more than 3 months, able to understand and speak English, with access to the internet and with no previous experience with WebEase were eligible to participate. Individuals were recruited through epilepsy-based websites and forums, on-line clinical research matching services and referrals from healthcare professionals. After informed consent, participants completed a baseline assessment and were randomly assigned to the intervention or wait list control condition. Participants assigned to the intervention condition began WebEase immediately after completing the baseline assessment, while those in the wait-list control condition waited 6 weeks and completed a second survey before beginning the WebEase program. Both groups completed a third survey 12 weeks after the baseline assessment. The three surveys measured epilepsy-related knowledge, self-efficacy, medication adherence, stress management, sleep time and quality, and quality of life.

Results: The study will conclude in August 2010. 191 participants were enrolled in the study and 45 participants were excluded because they did not meet the eligibility criteria. The average age is 40.68 (SD=13.18) with 89% of the participants self-reported as Caucasian/white. 74.3% are female. More than 77% of the participants have had some education beyond the high school level: 37% reported some college education or being currently in college, 28.1% completed a college degree and 11.9% reported a graduate degree. In May 2010, a preliminary data analysis showed improvement in epilepsy-related knowledge, medication adherence, stress management, sleep time and quality. Final data analysis will be available in September 2010.

Conclusions: Although the final results are not yet available, if the current results are maintained, evidence will be available to support the use of a self-paced, theory-based, online program in the support of self-management for people with epilepsy. This is important because the internet can be a viable option for promoting the health of people with epilepsy.

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TRENDS IN HEALTH CARE COST UTILIZATION, LENGTH OF STAY, IN-HOSPITAL MORTALITY AND DISCHARGE DISPOSITION IN PATIENTS HOSPITALIZED FOR EPILEPSY AND CONVULSIONS, 1993-2008

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Rationale: Background: The relationship of rising health care costs and trends in length of stay, in-hospital mortality and discharge disposition in patients admitted with epilepsy and convulsions is unknown.Our objective was to study sequential trends of health care costs, length of stay, mortality and discharge disposition of patients with epilepsy or convulsions. To determine if there is an association of health care costs trends and trends in length of stay, mortality and discharge disposition of patients with epilepsy or convulsions.

Methods: Using the National Inpatient Sample (NIS) health care utilization data from the Agency of Healthcare Research and Quality, we measured the sequential trends in health care cost, length of stay, inhospital mortality and disposition for all patients admitted between 1993 and 2008. Statistical analysis were done using (95% CI, $p<.05$). Z test was used to see difference in mean proportions and t test was used to see difference in means. The trends were tested using Pearson's correlation coefficient.

Results: Between 1993 and 2008, the number of discharges for the diagnosis of epilepsy and/or convulsions increased from 230245 to 277395 respectively. There was a 29 percent reduction in the mean duration of hospital stay from 4.9 days (±0.1) days in 1993 to 3.5 (±0.1) days in 2008 (95% CI, $p<0.001$). There was 58% reduction in in-hospital mortality between 1993 and 2008, a reduction from 1.48% (±0.07) in 1993 to 0.63% (±0.04) in 2008 (95% CI, $p<0.001$). Routine discharges to home decreased from 78.6%(±0.6) to 75.5% (±0.8) (95% CI, $p<0.01$) and discharges to a nursing home or rehabilitation hospital increased from 2.89% (±0.15) to 12.84%(±0.48)(95% CI, $p<0.001$. Patients requiring home healthcare increased from 4.5% (±0.23) in 1993 to 6.5%(±.025) in 2008(95% CI, $p<0.01$. The cost-charge ratio decreased by 59% from 0.75 in 2002 to 0.31 in 2008 (95% CI, $p<0.001$). The hospital charges per admission billed by hospitals tripled from $7,707 to $21,571 from 1993 to 2008. The trend of increase in hospital charges inversely correlated with inpatient mortality ($p<.03$) and length of stay ($p<.02$).

Conclusions: For patients admitted with epilepsy and convulsions, during the past 17 years, there seem to be statistically significant reductions in length of stay and in-hospital mortality. However proportion of patients requiring long term care increased. These changes have been accompanied by increases in health care utilization costs.

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DECREASING THE EPILEPSY TREATMENT GAP IN THE ECUADOR AMAZON REGION

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Rationale: In the Ecuador Amazon region, it is estimated that 70% of patients with epilepsy do not receive appropriate treatment due to lack of access to neurological diagnosis and care. The city of Tena is located in Napo in the rural Amazon region of Ecuador where the nearest facility with neurological services is located ~200 kilometers away. This distance and a substantial prevalence of poverty prevent patients from obtaining proper diagnosis and treatment of neurological conditions.

Methods: We have a sustained collaboration with staff and physicians of the local public Hospital Jose Maria Velasco Ibarra in Tena. We organized annual and quarterly epilepsy clinics. In April 2010, a team of 4 neurologists, 1 general practitioner, 1 electroencephalography (EEG) technician, 1 physical therapist and over 20 volunteers (medical students, nurses, and translators both from Ecuador, and the U.S.) examined patients in consultation with the internal medicine and pediatric staff of the hospital. Spanish and Quichua translation was available. Anti-epileptic drugs are supplied by the Ministry of Health free of charge. Members of the team lectured to local physicians, residents, medical students, first responders and the community on a variety of topics in epilepsy.

Results: In 3 working days, we evaluated a total of 350 patients with neurological complaints. Most of the patients were from urban and rural areas of the Napo Province, however some of them travel over 600 Km to be evaluated. Of the total number of patients evaluated, 122 had epilepsy, 54 % were children, 76 were new patients and 46 were follow-ups. Of the new patients with epilepsy, 43 had uncontrolled seizures and were receiving no treatment. A total of 36 EEGs were performed, 18 were normal, 10 with generalized epileptiform discharges, 5 with focal epileptiform discharges, and 3 with diffuse slowing. In response to the need for care of the patients with epilepsy, the hospital in collaboration with us created the first epilepsy clinic in this region, this will assure that patients with epilepsy will have continuity and follow up care.

Conclusions: A sustained ongoing collaboration with a rural hospital in the Ecuador Amazon region is decreasing the epilepsy treatment gap in this region. This ongoing project will continue to increase the access to epilepsy care in the developing world. Future efforts will aim at telemedicine consultation and educating local health providers in continuity of care for these patients with epilepsy.

IMAGE: images/905284_A.jpg

2010 Team Epilepsy Mission Tena, Ecuador

IMAGE: images/905284_B.jpg

Waiting Area Epilepsy Mission Tena, Ecuador 2010

2.361

KNOWLEDGE, BELIEFS, AND HEALTH CARE PERCEPTIONS OF EPILEPSY IN MINNESOTA'S NATIVE AMERICAN NATIONS

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Rationale: Epilepsy treatment results, especially in minority populations, are influenced by factors other than medications, e.g. knowledge level of the condition, beliefs of the ethnic/cultural group and community attitudes. Hereby we report on these factors on Native American(NA)subjects, i.e. Ojibwa, Lakota and Ho-Chunk, without epilepsy and compare it to non-native americans(NNA)also without epilepsy.

Methods: We administered a survey to 33 Native Americans (NA) randomly selected in NA community clinics in Minneapolis and University of Minnesota Neurology clinic, and compared it, using paired t-test, to 115 non-native American adults (NNA),also without epilepsy, and previously studied. The survey measured: knowledge of epilepsy, perception of the care people with epilepsy receive, and current spiritual and other beliefs concerning the condition.

Results: Significant difference between the two populations was seen in: 1) age, NA had a median age of 39 +/-14 compared to 48 +/-15 NNA, 2) female preponderance in NA, 82% NA vs 70%, perhaps reflecting NA population structure, Minnesota NA census, 2000, 3)marriage % was higher in NNA, and 4) secondary and post secondary education level and household income where lower in NA.

On items that measured knowledge, NA scored less correctly in etiology and also how to react to anticonvulsants side-effects and effectiveness.They scored equally on knowledge of heritability of epilepsy

A spiritual cause of epilepsy belief was higher in NA, although when adjusted for education and age was not significant (p=.08).

A less positive perception of health care dimensions, i.e. availability of neurology specialists, ancillary testing (EEG, MRI)and new drugs, was seen among NA, indicating a significant disparity.

In spite of the fact that knowledge level was less in NA, community acceptance of the condition was significantly higher for NA but trust of providers was,non-significantly, lower for NA.

Conclusions: The data suggests the need for: 1)additional education of NA on epilepsy causes, management 2)acceptance by NNA of the NA beliefs of a spiritual dimension to the condition, and 3)improving availability of specialized services and new medications to NA.

Of interest, the younger age of respondents in NA population may imply a trend towards more health care consciousness in the newer generations of NA, especially women, and suggests that lower levels of males accessing medical clinics, an ongoing issue across many populations, may be more prevalent in NA populations.

2.362

TRANSLATING RESEARCH TO PRACTICE: CDC MANAGING EPILEPSY WELL NETWORK

Rosemarie Kobau[1], C. K. DiIorio[2], Y. A. Bamps[2], N. Thompson[2], N. M. Clark[5], C. E. Begley[3], R. Shegog[3], R. T. Fraser[4] and P. Ciechanowski[4] ([1]Centers for Disease Control and Prevention, Atlanta, GA; [2]Emory University Rollins School of Public Heatlh, Atlanta, GA; [3]University of TX Health Sciences Center, Houston, TX; [4]University of Washington, Seattle, WA and [5]University of Michigan at Ann Arbor, Ann Arbor, MI)

Rationale: Living Well with Epilepsy I (1997) and II (2003)identified the need to improve social and behavioral science research for, and translation of, epilepsy self-management programs to improve quality of life in people with epilepsy (Living Well With Epilepsy II, 2004). CDC sought to translate these recommendations into an applied research program through development of the Managing Epilepsy Well Network.

Methods: In 2007, CDC funded the Managing Epilepsy Well (MEW) Network through its Prevention Research Centers. The MEW Network is composed of four Collaborating Centers(Emory Univ., Univ. of TX Health Science Center at Houston, Univ. of MI, Univ. of WA), CDC staff, affiliate members, Epilepsy Foundation (EF) affiliates and other community stakeholders. The MEW Network uses a Community of Practice Framework to guide its research agenda and its policies and procedures for collaboration. The mission of the MEW Network is to advance the science related to epilepsy self-management by facilitating and implementing research, conducting research in collaboration with network and community stakeholders, and broadly disseminating the findings of research.

Results: Since 2007, MEW Network members have been successful in developing and evaluating self-management interventions and depression treatment interventions; assessing stakeholder needs, collaborating with and communicating findings to stakeholders; and translating programs. Collaborating Centers have:

-Developed and evaluated a theoretically-based Internet program, WebEase (Web Epilepsy, Awareness, Education and Support)(DiIorio et al, 2009; 2009)

-Conducted research to examine socioeconomic differences in self-management and its impact on clinical outcomes in a cohort of epilepsy patients (Begley et al. 2008)

-Conducted formative research with chronic disease self-management and epilepsy stakeholders, and with adults with epilepsy to inform targeted and participant-driven self-management program development (Clark et al. 2010) http://www.sph.emory.edu/ManagingEpilepsyWell/documents/reports/Key_Informants_Perspectives_on_Managing_Epilepsy_v3.pdf

-Led the development of a decision-support tool for use in epilepsy clinics

Developed and pilot tested two community-based interventions (UPLIFT, PEARLS) for depression treatment

-Developed a multi-site intervention on epilepsy and depression prevention, funded in 2010 by the NIH Challenge Grant initiative

-Supported an external workgroup for the development of a measure of epilepsy self-management

-Launched the MEW website at http://www.sph.emory.edu/ManagingEpilepsyWell

-Provided training opportunities for implementing a community-based depression treatment intervention(http://www.pearlsprogram.org/)

-Applied the MEW model to extend activities related to the self-management of multiple sclerosis

Conclusions: The CDC Managing Epilepsy Well Network has been successful in conducting, disseminating, and translating epilepsy self-management research. The community of practice framework has been useful in fostering greater synergy across the MEW Network resulting in expanded research collaboration.

2.363

SURVEY OF NON-NEUROLOGISTS KNOWLEDGE OF DEPARTMENT OF MOTOR VEHICLES RULES AND REGULATIONS FOR LOSS OF CONSCIOUSNESS IN A MANDATORY REPORTING STATE

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Rationale: In the USA, different states have varying rules regarding mandatory reporting and counseling patients with recurrent events of loss of consciousness (LOC)and epilepsy. In six of the fifty states, including New Jersey, it is mandatory on the part of managing physicians to report these patients to the state Department of Motor Vehicles(DMV). Epilepsy is actually a rare cause of car crashes and accounts for approximately 0.2% of fatalities (Richards, K. Neurology 2004;63;E12). Other medical causes including diabetes, cardiovascular events, hypertensive disorders, asthma, and alcoholism have been found to be the more common causes of fatal car crashes. This survey evaluates the knowledge of New Jersey(NJ)non-neurologist physicians (NNPs)reporting patterns in this mandatory reporting state.

Methods: This IRB approved pilot survey was undertaken to evaluate the knowledge of practicing NNPs in NJ of DMV rules and regulations for patients with serial events of LOC. We asked whether the NNPs were aware that NJ is a mandatory reporting state and if they have followed these mandates (reporting patients to the state). Physicians and physician assistants at two tertiary care hospitals in central New Jersey anonymously completed a six question survey. Questions asked included the number of years practiced in NJ, whether they treat patients with recurrent events of impaired consciousness, knowledge that NJ is a mandatory reporting state and their reporting practices.

Results: Seventy one NNPs were surveyed all of whom practiced an average of 13 years (range 1-40 yrs). NNPs included the following: cardiologists, ED physicians, family physicians, internists, pulmonary specialists, and endocrinologists. 75% of NNPs had patients with two or more events of LOC in a year. 38% of NNPs knew that NJ was a mandatory reporting state. 32.4% knew that patients with recurrent events of LOC need freedom from LOC events for one year before driving privilege reinstatement. Only 22.2% of these NNPs ever reported their patients to the DMV.

Conclusions: Though epilepsy is a rare cause of fatal and nonfatal car crashes, other medical causes are more common. Only about one third of NNPs surveyed knew that NJ is a mandatory reporting state. Of the NNPs who saw patients with recurrent periods of impaired consciousness, a mere 22.2% reported these patients to the state DMV. A recent study found neurologists reporting in NJ to be 35% (Drazkowski et al. AES Abst. 1.130, 2009). With such low reporting rates and so few NNPs knowing these laws in general, it calls into question the utility of these mandatory reporting statutes and their effectiveness. In addition, the fact that these laws are not uniform from state to state may also further complicate matters. NJ DMV rules and regulations are more stringent and seem ignored by many NNPs and neurologists. Educating NNPs and neurologists regarding the state laws and increased patient counseling of the risks of impaired driving may indeed help improve public safety.

2.364

DISOBEDIENCE AND DRIVING IN PATIENTS WITH EPILEPSY

William O. Tatum[1] and M. B. Selenica[2] ([1]Neurology, Mayo Clinic College of Medicine, Mayo Clinic Florida, Jacksonville, FL and [2]Pharmacology and physiology, University of South Florida, Tampa, FL)

Rationale: Driving is important to patients with epilepsy (PWE) and allows for optimal quality of life. Driving is prohibited when PWE are not seizure free as motor vehicle accidents (MVAs) may result from breakthrough seizures due to drivers with epilepsy (DWE). Despite state driving restrictions for PWE, many continue to drive. We sought to characterize DWE that intend to be disobedient with driving laws.

Methods: A 12-question survey was delivered to 287 consecutive PWE at a single outpatient epilepsy clinic in Florida. Participation was voluntary and surveys were completed around the time of clinical visitation and evaluated at study completion. 236 surveys were evaluated (age and gender included) and 51 were not due to incomplete information or alternate primary diagnosis. Following informed consent, PWE were prospectively surveyed between 11/08 and 2/09. Responses were retrospectively reviewed for disobedient DWE that negatively responded to the question; “Do you plan to wait the entire length of time before you are informed that it is okay to resume driving?”. All questions were multiple choice questions or yes-no responses. The survey format included information on demographics, driving, last seizure, number of lifetime seizures, AEDs, emotional reaction to restriction, and awareness of the driving restrictions for PWE.

Results: 182/236 (77.1%) PWE (144 F) responded “yes” and would wait before driving but 27 (11.4%) said “no”, 15 (6.4%) did not respond, 9 (3.8%) responded “NA” (1 checked both, 1 responded “?”, and 1 wrote “seizure free”). The “disobedient” 27 DWE (16 F) were aged 49.9 years (range 21-80 y), were primarily Caucasian (n=21), with epilepsy in 24/27 cases (3 reported 1 seizure). 14/27 (51.9%) had >20 seizures in their lifetime. The last seizure was < 6 months in 23/27 (85.1%). 20/27 (74.0%) did not comply, 16/27 (59.3%) drove “wherever they needed to go” but only 4/27 self-reported non-compliance with AEDs (p=0.006). Most patients (16/27) took a single drug, 8 were on 2, 1 was on 4 AEDs, 1 had VNS (1 not taking AEDs). 24 held valid licenses (22 from FL), and nearly 2/3rds (17/27=63.0%) knew the restriction.

26/27 PWE had a negative reaction to restriction (3 with > 1 reaction), and only 1 felt relieved when told (p=<0.0001). 8/27 (29.6 %) denied having the law discussed with them despite written attestation in all. Informed DWE 16/19 (84.2%) knew the law in contrast to 1/8 (12.5%) “uninformed” DWE (p=0.12). In contrast to sadness which was reported in the group as a whole (75/236), anger (8/27) was the most common initial impulse to restriction in disobedient DWE. Only 7/27 (25.9%) had an initial impulse to wait v 198/236 (83.9%) of the group (p=0.006).

Conclusions: 11.4% of PWE are disobedient with state restrictions for DWE and 85.1% are ineligible. Most non-compliant DWE will report compliance with their AEDs. PWE feel a negative reaction to driving restrictions, and anger, initial rejection of the legal restriction, and denial of being informed about the driving laws are red flags that predict disobedience.

2.365

REVISING PROJECT UPLIFT FROM A TREATMENT INTERVENTION TO A PREVENTION INTERVENTION

N. J. Thompson[1], A. L. Edwards[1], A. Garcia-Williams[1], R. T. Fraser[2], C. E. Begley[3] and L. M. Selwa[4] ([1]Department of Behavioral Sciences and Health Education, Emory University, Atlanta, GA; [2]Neurology, Neurological Surgery, & Rehabilitation Medicine, University of Washington/Harborview Medical Center, Seattle, WA; [3]School of Public Health, The University of Texas Health Science Center, Houston, TX and [4]University of Michigan, Ann Arbor, MI)

Rationale: Depression affects over 19 million people in the United States, and is more frequent among those with chronic illnesses like epilepsy. Jones et al.13 reported that up to 48% of people with epilepsy are depressed. Funded by the Centers for Disease Control and Prevention (CDC) as a home-based treatment for people with epilepsy, Project UPLIFT (Using Practice and Learning to Increase Favorable Thoughts) was originally developed to provide group delivery of depression treatment by telephone or Web. Materials were based upon both cognitive-behavioral therapy and mindfulness. Recently, the National Institutes of Health provided funding through the Challenge Grant Initiative to: 1) revise the Project UPLIFT materials for use preventing depression, rather than treating it; and 2) estimate the effectiveness of the revised materials. This paper will focus on what we encountered in creating a version of Project UPLIFT for use in prevention.

Methods: The curriculum was revised with language and content modified for prevention, and feedback was obtained from epilepsy experts collaborating on the project. Focus groups were then co-facilitated by a graduate student and a person with epilepsy to formatively evaluate the revised curriculum. They were audio recorded and data transcribed and qualitatively analyzed. All participants had taken part in the treatment version of Project UPLIFT. Results of recruiting for the prevention intervention were also explored.

Results: Language and content modifications for prevention required revisions such as referring to as “low mood” or “feeling blue,” rather than depression. Coping was discussed in terms of precursors of depression, (e.g., stress) instead of depression itself. Skills were framed as means of keeping from becoming depressed, rather than directly addressing depression. Sessions on finding pleasure were emphasized, and preventing relapse into depression was modified to preventing relapse into old, unhealthy behaviors (e.g., negative thinking). Focus group participants perceived the changes to the curriculum to be acceptable, but suggested simplifying several exercises, establishing real-time contact in the Web group, and clarifying that epilepsy was only one of many factors in their lives that can lead to depression. Recruiting results indicated that many people with epilepsy were already depressed, making prevention impossible.

Conclusions: The resources found to be effective in treating depression among people with epilepsy were successfully adapted for prevention. The changes to the materials were well accepted by people with epilepsy, but it is important to continue simplifying them to improve their usability and adoption. More research is needed to determine the onset of depression relative to epilepsy, as there is difficulty reaching participants before they are depressed, allowing for prevention.

2.366

EPILEPSY AND EPILEPSY SURGERY NEWLY CHARACTERIZED IN A 1950 FILM

Diane B. Friedman (St. Vincent Neuroscience Institute, Indianapolis, IN)

Rationale: The neurologist and neurosurgeon Tracy J. Putnam MD was a pivotal figure in epilepsy and neurosurgery. It is widely known that in 1937 he was co-developer, with H. Houston Merritt, of phenytoin, and director of the New York Neurological Institute, 1939-19471. He was also a technical advisor concerning the neurological and neurosurgical aspects of the 1950 film Crisis2 starring Jose Ferrer and Cary Grant. The neurological and neurosurgical aspects of this film have never been explored in medical or cinema literature.

Methods: Successive versions of original scripts and other primary documents show Putnam's input to the script3. He and a surgical nurse from his neurosurgical team at Cedars of Lebanon Hospital in Los Angeles were on the set to coach Grant in surgical techniques and were present on the set during surgical scenes. Grant and Richard Brooks attended several surgeries performed by Putnam.

Results: This film depicts the kidnapping of American neurosurgeon Eugene Norland(Grant) while on his honeymoon in South America. He is brought to the mansion of the dictator Raoul Ferrago (Ferrer) who is shown having a complex partial seizure with secondary generalization. He has a visual aura (a cheering throng) in his right visual field while having simultaneously a right hemianopsia. He has papilledema and right arm drift. He is diagnosed with a left temporal meningioma and surgery is performed in the mansion because the dictator has too many enemies to risk going to a hospital. The surgeon is caught between caring for a patient he does not respect while resisting the pleas of revolutionaries who would like the surgeon to let his patient die. The film depicts several contemporary surgical techniques including the use of drawings in which landmarks of the left temporal lobe and sylvian fissure is clearly visible.

Conclusions: New developments in antibiotics, neurosurgical technique, anesthesia delivery, and antiepileptic medications in the previous 10 years made it possible to use seizures as a device to explore the dramatic situation of a neurosurgeon holding in his hands the possibility of letting his dictator patient die for the good of the country or to save the dictator in order to also save his wife's life. This mirrored situations during the regime of Joseph Stalin, who called several surgeons, including Herbert Olivecrona to care for him or a member of his political cabinet. Actually, in the original story for the film written by George Tabori3, Olivecrona is mentioned specifically several times as an example of a physician who did his best for every patient despite his life choices. Tracy Putnam's expert and unrecognized contribution of neurological accuracy contributes to the realism and intensity of the situation in the film and permits the dramatic irony of the story of a murder with no murderer.

1. Rowland, LP. The Legacy of Tracy J. Putnam and H. Houston Merritt. Oxford: Oxford University Press, 2009.

2. Crisis MGM 1950. Directed by Richard Brooks; from a story by George Tabori.

3. Original papers Crisis, Margaret Herrick Library, Academy of Motion Picture Arts and Sciences, Los Angeles.

Sunday, December 5, 2010

Investigators' Workshop Sunday Morning Session I
8:45 a.m.-10:15 a.m.

IW.03

EPIGENETIC MECHANISMS OF EPILEPTOGENESIS

Christophe Bernard (INSERM, Marseille, France)

Summary: Epileptogenesis, the process leading to epilepsy, can be triggered by a brain insult such as brain trauma, status epilepticus or long febrile seizures. The initial insult produces complex alterations in the neuronal circuitry. These include down- and up-regulation of hundreds of genes, that are often long-lasting. Changes in gene expression could thus play a central role in the construction and maintenance of epileptogenic networks. This workshop focuses on the mechanisms by which epileptogenic insults provoke enduring changes in gene expression. Interfering with these mechanisms may be disease-modifying.

Regulation of chromatin structure is a principle means of controlling gene expression in eukaryotes. The transcriptional repressor NRSF/REST controls many genes in the central nervous system involved in plasticity and disease, via chromatin structure modification. NRSF can potentially alter the expression of ~1800 genes that possess the cognate NRSE sequence.

Dr. Baram will discuss the role of the NRSF/REST in epileptogenesis triggered by status epilepticus. She will focus on epigenetic effects of this repressor, on the emerging 'minimal set' of 'epileptogenic genes', and on the use of NRSF/REST as a molecular target for aborting epileptogenesis.

If NRSF/REST is central to epileptogenesis, its actions should be model-independent. Dr. Dingledine will present findings obtained using an epilepsy microarray consortium formed to identify model-independent changes in gene expression in dentate gyrus granule cells following three types of status epilepticus that lead to epileptogenesis. Differentially-expressed genes were highly enriched in NRSF/REST targets, pointing to a broad role for the REST/NRSE system in driving transcriptional responses to epileptogenesis.

Importantly, the NRSF/REST gene itself is also regulated. Alternative splicing occurs after seizures, resulting in a truncated altered-function variant of NRSF termed REST4. Dr. Roopra will describe the mechanisms by which REST splicing is controlled and how this effect impacts neuronal gene expression.

IW.04

THE ENDOCANNABINOID SYSTEM AND TEMPORAL LOBE EPILEPSY

Astrid Nehlig[1], Zsofia Magloczky[2], Karolien Goffin[3], Robert DeLorenzo[4] and Ivan Soltesz[5] ([1]INSERM U 666, Strasbourg, France; [2]Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary; [3]Nuclear Medicine, Faculty of Medicine, Leuven,

Belgium; [4]Neurology, Virginia Commonwealth University, Richmond, VA and [5]Anatomy and Neurobiology, UCI, Irvine, CA)

Summary: The endocanabinoid system is an important neuromodulatory system that regulates cognition, learning and memory, motor behavior and pain perception. Upon depolarization of a postsynaptic neuron, endocannabinoids are released in the synaptic cleft, bind to the presynaptic type 1 cannabinoid receptor (CBR1) leading to a decrease in neuronal excitability. This mechanism is a key regulator of neurotransmission in the normal brain but might play a critical role in providing 'on-demand' protection against pathologic hyperexcitability and seizures. Several recent studies seem to confirm the anticonvulsant role of the endocannabinoid system and reported that a neuroprotective machinery involving endocannabinoids is impaired in the hippocampus of human epileptic patients leading to the hypothesis that the downregulation of CBR1 and related molecular components of the endocannabinoid system may increased network excitability. One focus of this workshop will be to clarify the present knowledge of the distribution of CBR1 in the brain of healthy human subjects and how the availability of these receptors changes both in epileptic patients and in animal models of temporal lobe epilepsy. Furthermore, in animal models of temporal lobe epilepsy the endocannabinoid system was shown to undergo time-dependent changes related to the evolution of seizure activity. Altogether, data using imaging, neuropathologic and molecular approaches will be presented. Finally, these data will be discussed in light of the major functional characteristics of endocannabinoid signaling in the modulation of synaptic activity in the normal and epileptic brain. A better knowledge of how this system regulates neuronal excitability might lead to new therapeutic avenues for the treatment of drug-resistant epilepsy.

IW.05

MAPPING BRAIN NETWORKS IN EPILEPSY: INSIGHTS FROM NOVEL EEG, FMRI AND MORPHOMETRIC MRI METHODS

Andrea Bernasconi[1] and William D. Gaillard[2] ([1]Neurology and Neurosurgery, Montreal Neurological Institute, Montreal, QC, Canada and [2]Neuroscience, Children's National Medical Center, Washington, DC)

Summary: The human brain is anatomically and functionally organized into complex networks allowing both segregation and integration of information. During the last decade, multidisciplinary research in neuroimaging has provided methods capable of exploring in vivo and non-invasively both structural and functional connectivity at the macroscopic level. These methods are of particular interest to epilepsy since large-scale brain networks connectivity is responsible not only for high cognitive processes, but also for the clinical manifestations of this condition. Studying networks is also crucial to understand consequences of the epileptic process, and its relationship to brain morphology and function.

This workshop will assemble a panel of experts that have proposed novel frameworks based on EEG, functional and structural MRI to assess quantitatively brain connectivity. It will provide participants with: the principles of recent EEG and MRI methods to analyze brain networks; a comprehensive review of data on in vivo mapping of temporo-limbic and cognitive networks; a multidisciplinary discussion on the pathophysiology of epileptogenic networks remodeling, with emphasis on temporal lobe epilepsy.

Novel methods that have provided independent evidence for altered connectivity in epilepsy will be discussed: analysis of spatial properties of EEG signal and resting state fMRI analyzing temporal correlations of BOLD signals (Dr M. Guye, University of Marseille, France); fMRI activation studies mapping functional networks associated with memory and language (Dr M Berl, George Washington University School of Medicine, USA); analysis of structural connectivity using MRI-based morphometric correlational data (N. Bernasconi, Montreal Neurological Institute, McGill University, Canada).

Sunday, December 5, 2010

Investigators' Workshop Sunday Morning Session II
10:30 a.m.-12:00 p.m.

IW.06

THE EMERGING ROLE OF THE AXON INITIAL SEGMENT IN EPILEPTOGENESIS

Verena Wimmer[1], Edward C. Cooper[2] and Matthew N. Rasband[3] ([1]Ion Channels and Disease, Florey Neuroscience Institutes, Melbourne, VIC, Australia; [2]Department of Neurology, University of Pennsylvania, Philadelphia, PA and [3]Department of Neuroscience, Baylor College of Medicine, Houston, TX)

Summary: Information processing in neurons relies on the integration of excitatory and inhibitory inputs to encode action potential (AP) firing. In most neurons the "program" that determines AP firing resides within the axon initial segment (AIS), a specialized domain of the axon proximal to the soma. The AIS has been increasingly in the spotlight as studies unravel the molecular basis of its functional and cell biological complexity, from AP initiation to disease and excitability dependent structural plasticity.

The primary goal of this workshop is to highlight the role of the AIS in epileptogenesis. AIS function is dependent on clustering of a multitude of different ion channels, an intriguing number of which have been associated with human genetic epilepsy. Furthermore, recent evidence of activity dependent structural plasticity potentially implicates the AIS more generally in the pathology of epilepsy.

Prof Rasband will start the session with an overview of the molecular anatomy of the AIS and discuss ideas and data on AIS-specific pathogenic mechanisms in neuronal injury. Prof Cooper will present functional studies on the vital role of potassium channels in the AIS in health and disease and Dr Wimmer will provide direct evidence for AIS-based pathogenic mechanisms in genetic epilepsy. Together, these three presentations will provide an overview of recent advances in the understanding of AIS dysfunction in neuronal pathogenesis. A secondary goal of the workshop is to stimulate discussion of future research on the role of AIS in epilepsy and its potential as a therapeutic target.

IW.07

NEUROBIOLOGICAL MECHANISMS IN GENETIC FOCAL EPILEPSIES: THE CASE OF LGI1

Ruth Ottman ([1]G. H. Sergievsky Center, Columbia University, New York, NY and [2]Departments of Epidemiology and Neurology, Columbia University, New York, NY)

Summary: This workshop will discuss clinical and molecular approaches for study of the mechanisms of epileptogenesis in focal epilepsies, using research on the leucine-rich, glioma inactivated 1 gene

(LGI1) as a model. Mutations in LGI1 have been identified in up to half of families with autosomal dominant partial epilepsy with auditory features (ADPEAF), a genetic focal epilepsy syndrome with auditory symptoms and receptive aphasia as major ictal manifestations. These symptoms strongly suggest localization to the lateral temporal lobe; hence the syndrome is also called autosomal dominant lateral temporal lobe epilepsy (ADLTE). Unlike most other genes identified in Mendelian forms of epilepsy, LGI1 has no homology to any ion channel. The mechanism by which mutations influence susceptibility to epilepsy has been unclear, but recent studies have made important progress in elucidating this mechanism. In the workshop we will present the latest findings and discuss the experimental approaches used in these investigations.

IW.08

INSIGHTS FROM NEUROIMAGING ON BRAIN DEVELOPMENT IN CHILDREN WITH "EPILEPSY ONLY"

Rochelle Caplan[1], Bruce Hermann[2] and Hal Blumenfeld[3] ([1]Department of Psychiatry, UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, CA; [2]Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison, WI and [3]Department of Neurology, Neurobiology, Neurosurgery, Yale University School of Medicine, New Haven, CT)

Summary: Children with epilepsy with average intelligence but without neurological handicaps and neuroradiological abnormalities have frequent cognitive, linguistic, and psychopathology comorbidities, However, the structure, function, and underlying neural mechanisms of brain development in the children with and without these comorbidities, an NINDS "comorbidity benchmark," remain unclear and a subject of both clinical and basic science research.

This workshop will bring together researchers on comorbidities, neuroimaging, and basic science to integrate the comorbidity and multimodal neuroimaging findings in these children with cognitive and behavioral impairments evident in animal models of seizures. To do this, Bruce Hermann will describe baseline and prospective volumetric and morphometric findings and their association with cognition in children with recent onset epilepsy with and without comorbidities. Rochelle Caplan will discuss volumetric, morphometric, and MRS data related to a broad range of psychopathology in children with epilepsy. Hal Blumenfeld will relate ictal fMRI, interictal DTI, and resting functional connectivity in childhood epilepsy, as well as fMRI network abnormalities to direct neuronal recordings in animal models of childhood epilepsy. Integrating the findings of the presenters, the general discussion will focus on how to model comorbidities of epilepsy in animals to study the neurobiological connection.

Delineation of the mechanisms underlying the comorbidities of pediatric epilepsy is essential because of their role in the lifelong morbidity the illness. The proposed workshop would be a first step towards integrating the findings of research at the behavioral, neuroimaging, and neuronal level to better understand how impaired cognition and behavior reflect the complex effects of the illness (above and beyond the effect of seizures) on neuronal function, neural circuits and connectivity, and microstructural abnormalities. Furthermore, examining the effects of seizures on multiple aspects of brain structure and function will prove essential in developing future translational studies to clarify why children with "epilepsy only" exhibit cognitive deficits and psychopathology.

Sunday, December 5, 2010

Investigators' Workshop Poster Session - Lunch Session
12:00 p.m.-1:30 p.m.

1.002

THE ROLE OF ASTROCYTES IN THE EPILEPTOGENICITY OF CORTICAL MICROGYRI

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Rationale: Developmental cortical malformations including polymicrogyria and tuberous sclerosis are associated with intractable epilepsy. To understand the pathophysiology of epilepsies associated with cortical malformations, we have utilized glutamate imaging in the freeze-lesion (FL) model of polymicrogyria. In this model neurons that form deep cortical layers are lost, resulting in a microgyrus enriched in layer II/III neurons. Our preliminary findings have shown that the ability of glial cells to remove applied extracellular glutamate is altered in the FL model. Regional differences in glutamate reuptake were measured using glutamate imaging and SR101 staining was used to quantify the location of astrocytes in and around the lesion site. Immunohistochemical analysis of multiple glial cell markers was also used to examine the local density and phenotype of astrocytes in the malformed cortex.

Methods: Microgyri were created by briefly placing a freezing probe on the skulls of neonatal rat pups. Neocortical brain slices from sham operated and freeze lesioned rats were prepared 14-128 days later. Brain slices were then loaded with glutamate FRET biosensor and both images and extracellular field recordings were collected simultaneously. Brain slices were also stained with SR101, an astrocyte specific dye for use in live tissue, and maps of glial density were made using in-house imaging software.

Results: In order to thoroughly address the regional variability in glutamate reuptake capacity we locally perfused 5 mM glutamate onto the microgyral zone (MZ). Glutamate reuptake capacity was increased in the MZ itself while in areas adjacent to the MZ glutamate reuptake capacity was compromised. As predicted, glutamate reuptake capacity was directly correlated to glial cell density as measured by SR101 staining. In regions where glial cell density was highest there was a higher capacity to remove applied glutamate. This correlation was lost when TBOA, an antagonist of the plasma membrane glutamate transporters, was applied to the tissue before perfusion of glutamate. Immunohistochemical analysis of GFAP, ALDH1L1, a pan-glial marker, and GLT-1, the astrocytic glutamate transporter, was performed. Interestingly ALDLH1 and GLT-1 appear to be increased in the MZ where glutamate reuptake capacity was highest and GFAP staining was more abundant directly adjacent to the MZ, where glutamate reuptake capacity was lower.

Conclusions: Our findings indicate that there are anatomical and functional changes in astrocytes in the FL model. The decrease in glutamate reuptake capacity directly adjacent to the MZ and the increased expression of GFAP in this area suggests that reactive astrocytes cannot efficiently clear synaptically released glutamate. This may in turn lead to prolonged glutamate signaling and contribute to the hyperexcitability of the FL. The increase in astrocytic protein expression and regional glutamate uptake within the MZ, on the other

hand, suggests that the increased density of glia in the MZ may contribute to more efficient glutamate clearance within this region.

1.010

ALTERED GABA SIGNALING IN THE ACUTE HIPPOCAMPAL SLICE MODEL OF BRAIN TRAUMA

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Rationale: Traumatic brain injury is often complicated by early seizures occurring within the first week after injury. These early seizures may exacerbate the brain injury increasing the risks for development of epilepsy. The mechanisms underlying early post-traumatic seizures remain unknown.

Methods: High resolution two-photon fluorescence chloride imaging and simultaneous non-invasive extracellular field potential recordings of multiple unit activity (MUA) and synchronous population activity were performed in the intact hippocampus and acute hippocampal slices in vitro of the neonatal (postnatal day (P) 5-7) transgenic mice CLM-1 expressing Clomeleon. Acute hippocampal slices were used as a model of severe traumatic brain injury. Age-matched intact hippocampal preparations from the same animals were used as controls. Simultaneous extracellular field potentials of multiple unit activity from hundreds of neurons were performed to determine whether the net responses to $GABA_A$ receptor modulators are excitatory or inhibitory.

Results: Using two-photon microscopy and the genetically expressed chloride fluorophore Clomeleon, we found that neurons in brain slices from neonatal CLM-1 mice exhibit a profound accumulation of $[Cl^-]_i$, resulting in long-term shift in the reversal potential for $GABA_A$ receptor mediated responses (E_{GABA}). The $[Cl^-]_i$ accumulation inverted the net operation of $GABA_A$-receptor from inhibition to excitation. There was a very strong correlations between neuronal $[Cl^-]_i$ and proximity to the slice surface. The $[Cl^-]_i$ of many morphologically normal neurons near the surface was high enough to cause E_{GABA} to be positive to action potential threshold. For the cells with highest $[Cl^-]_i$ (> 100 mM) there was also a strong correlation between $[Cl^-]_i$ and neuronal volume, with large swollen cells exhibiting $[Cl^-]_i$ close to the chloride concentration of the extracellular solution. There was also a strong correlation between neuronal $[Cl^-]_i$and the probability of apoptosis as assayed by fluorescent indicator of caspase activation (FLICA). Inhibition of neuronal NKCC1-mediated inward chloride transport with the diuretic bumetanide did not reduce $[Cl^-]_i$ in the most of large swollen neurons.

Conclusions: Our results provide a possible mechanism for early pathological GABA-mediated excitation after traumatic brain injury. We are currently investigating the long-term chronic effects of neuronal trauma and intracellular chloride accumulation on development of spontaneous epileptiform discharges and anticonvulsant resistance.

1.014

MTOR INHIBITION HAS POTENTIAL ANTIEPILEPTOGENIC EFFECTS IN A CONTROLLED CORTICAL IMPACT MODEL OF TRAUMATIC BRAIN INJURY

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Rationale: Traumatic brain injury (TBI) is a major cause of disability and death. TBI is often accompanied by the subsequent development of posttraumatic epilepsy (PTE). Seizures of PTE are frequently intractable to available treatment options and attempts at preventing PTE have been unsuccessful. Understanding basic mechanisms of posttraumatic epileptogenesis is important for developing antiepileptogenic therapeutic approaches to PTE. The mammalian target of rapamycin (mTOR) pathway has been implicated in mediating mechanisms of epileptogenesis in other models of epilepsy and has also been reported to be activated in models of TBI. In this study, we tested the hypothesis that mTOR inhibition may have antiepileptogenic actions in the controlled cortical impact (CCI) model of experimental TBI.

Methods: Adult male CD-1 mice received a craniotomy and a single episode of TBI to left lateral cortex using an electromagnetic CCI device with an injury depth of 2.0 mm. Control mice received sham surgery with a left craniotomy only. Rapamycin (6mg/kg/d, i.p.) or vehicle was initiated 1 hour after TBI and continued for 3 weeks. Western blot analysis of P-S6 expression in left hippocampus and neocortex was performed at various time points (1h, 3h, 6h, 24h, 3d, 1w, 2w, 3w) after TBI or sham surgery, and effects of rapamycin versus vehicle on P-S6 expression was also tested at 6h and 3d after TBI. Histological analysis of neuronal death by Fluoro-Jade B staining and mossy fiber sprouting by Timm's staining was performed at 3d and 1w, respectively, after sham surgery or TBI in vehicle- and rapamycin-treated mice. Video-EEG recordings monitored for seizures up to 16 weeks after TBI in vehicle- and rapamycin-treated mice.

Results: mTOR pathway activation, as reflected by P-S6 expression, was significantly increased following TBI in both hippocampus and neocortex. This increase in P-S6 expression started at 3h, peaked at 6h and then decreased within 1w, returning to baseline by 2w after TBI. Rapamycin, administered after TBI, significantly blocked mTOR activation at 6h and 3d, and decreased neuronal death and mossy fiber sprouting in hippocampus. Initial video-EEG studies suggest that rapamycin decreases the development of spontaneous seizures during the first couple of months following TBI, although continued monitoring is ongoing to determine the long-term effects of rapamycin on PTE.

Conclusions: The mTOR pathway is strongly activated following experimental TBI and may mediate mechanisms of epileptogenesis in the CCI model of TBI. The mTOR inhibitor rapamycin may have antiepileptogenic effects in this model. Supported by NIH NS056872.

1.018

KAINATE-INDUCED STATUS EPILEPTICUS ALTERS BDNF GENE EXPRESSION IN AREA CA1 AND MEMORY FORMATION USING EPIGENETIC MECHANISMS

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Rationale: Brain-derived neurotrophic factor (BDNF) has been identified as a possible molecular mediator in epileptogenesis and in memory formation. However, little is known about the regulation of the bdnf gene in the CNS. We hypothesize that aberrant expression of memory-related genes, such as bdnf, contribute to deficits in hippocampus-dependent long-term memory formation associated with prolonged seizure activity. The studies presented here expand on the idea that epigenetics, a new molecular mechanism for gene expression changes in the nervous system, may play a role in memory disorders associated with epilepsy. For our studies we focused on area CA1 of hippocampus, a brain region well-characterized in the process of contextual long-term memory storage.

Methods: First, we determined the pattern of post-translationally modified histones (Chromatin Immunoprecipitation) and DNA methylation (Bisulfite Sequencing) at the bdnf gene in area CA1 of hippocampus after 1 h of kainate (KA)-induced status epilepticus (SE). We next determined the expression of exon-specific bdnf mRNA levels in hippocampus following KA-SE. Finally, using a contextual fear conditioning learning paradigm, we assessed the effect of histone deacetylase inhibition (HDACi) on long-term memory formation in epileptic animals (2-3 months post-SE).

Results: Quantitative real-time PCR revealed significant increases in exons I, II, IV, VI and IX bdnf mRNA levels in area CA1 of hippocampus at 1 h of KA-SE. These results support previous findings that exon-specific bdnf gene regulation occurs in hippocampus following KA-SE. Interestingly, we found that alterations in hippocampal bdnf mRNA levels correlated with DNA methylation changes at the bdnf gene during SE. Specifically, we observed demethylation of the bdnf gene at a CpG island within bdnf promoter 4 in area CA1 after 1 h of KA-SE. Next, we examined whether histone modifications at bdnf promoters, another epigenetic mechanism directly implicated in bdnf gene regulation, was altered in area CA1 of hippocampus during SE. We found that both histone H3 acetylation and phosphoacetylation levels increased at bdnf promoter 4 in area CA1 of hippocampus after 1 h of KA-SE. Moreover, HDACi with sodium butyrate significantly altered SE-induced bdnf gene expression changes in area CA1 of hippocampus at 1 h or 24 h after KA-SE and HDACi significantly enhanced long-term memory formation in epileptic animals.

Conclusions: Together our findings suggest that epigenetic regulation of the bdnf gene during epileptogenesis, mechanistically via histone modification and DNA methylation, may mediate long-lasting behavioral changes in epilepsy. Indeed, our present findings suggest that HDACi improves fear memory processing in animals that had experienced epilepsy. Additional studies are underway for assessment of altered DNA methylation patterns at the bdnf promoters in hippocampus during fear memory consolidation after KA-SE.
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1.029

REGIONAL DIFFERENCES IN ARC/ARG 3.1 PROTEIN EXPRESSION IN THE IMMATURE BRAIN INDUCED BY SEIZURES

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Rationale: Activity-regulated cytoskeletal associated protein (Arc/Arg 3.1) is an immediate-early gene that is rapidly induced by neuronal activity. Arc/Arg3.1 is known to be required for long-lasting forms of synaptic plasticity, learning and memory consolidation. It has been demonstrated that Arc/Arg3.1 selectively regulates trafficking of AMPA-type glutamate receptors (AMPARs) in neurons by accelerating endocytosis and reducing surface expression of GluR2 and GluR3 subunits. We have previously shown that AMPA receptor trafficking is critical to enhanced network excitability following early life hypoxia-induced seizures (HS) in a rat model of neonatal seizures. We hypothesized that Arc/Arg 3.1 activation may be upstream of AMPA trafficking, which occurs between 1-24 hours after seizures. In the present study we evaluated the temporal and spatial pattern of Arc/Arg 3.1 expression in postnatal day (P)10 rats in which seizures were induced either by hypoxia or by pentylenetetrazol (PTZ).

Methods: Seizures were induced in male Long Evans rats at P10 either by exposure to graded global hypoxia (15 min to min of 4%O2) (n=4) or PTZ dose (80 mg/kg i.p.) (n=4). Untreated littermates were used as controls (n=2). Rat pups were perfused 2, 4 or 6 hours after seizure onset. 20 μM sections were cut from fixed brains and immunostained with Arc/Arg 3.1 antibody (sc-15325, Santa Cruz Biotechnology).

Results: Minimal baseline staining of Arc/Arg 3.1 was seen in the cortex and hippocampus in the P10 controls. As early as 2 hours after PTZ injection, Arc/Arg 3.1. neuronal staining was more intense and widespread in the cortex (cingulate cortex, retrosplenial cortex, neocortical layers II-VI and subplate), hippocampus (CA1, CA3 and dentate gyrus), pyriform cortex and hypothalamus (anterior hypothalamic area, arcuate nucleus, dorsomedial and ventromedial). In comparison, at 2 hours after HS, only slight staining was seen in layer II of the cortex, subplate and pyriform. By 4 or 6 hours, immunoreactivity increased and staining was present in the same regions as PTZ-induced seizures. However, hypoxic seizures resulted in a more intense staining in the pyriform cortex, thalamus and hypothalamus (arcuate nucleus, dorsomedial and periventricular).

Conclusions: These results suggest a change in Arc/Arg3.1 expression induced by seizures in the immature brain. Further studies are required to understand the molecular pathway that relates Arc/Arg3.1 protein with AMPARs.

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1.031

RAPID LOSS OF DENDRITIC HCN CHANNEL EXPRESSION FOLLOWING STATUS EPILEPTICUS

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Rationale: Hyperpolarization-activated cyclic nucleotide-gated (HCN) ion channels are voltage-gated ion channels expressed in hippocampal and neocortical pyramidal neuron dendrites that diminish excitability. We and others have demonstrated the loss of expression and downregulation of gating of HCN channels during the development of epilepsy following status epilepticus (SE): the density of I_h, the current mediated by HCN channels, declined to 40-50% of control levels by 1 wk after pilocarpine-induced SE, along with an ~50% loss of HCN1 protein expression (Jung et al., 2007; 2010). Both remained decreased at 3-5 wk in chronically epileptic animals, while loss of HCN1 mRNA expression began at 3 d post-SE and persisted at 30 d (Marcelin et al., 2009). In the present study, we sought to characterize the acute timecourse of the post-SE decrease in I_h, and its molecular correlates.

Methods: Dendritic cell-attached patch clamp recordings in CA1 hippocampal neurons were obtained in brain slices from rats after pilocarpine-induced SE, along with Western blotting for HCN1 protein, and real-time RT-PCR for HCN1 mRNA.

Results: At 1 h post-SE, I_h was significantly decreased compared to control levels (all values reported as % of control), with I_h at maximal activation reduced to 50 ± 2.0 %, $p<.01$ vs. control), while HCN1 protein (95 ± 3.0 %) and mRNA levels (98 ± 11 %) were unchanged. At 1 d post-SE, I_h declined further (27 ± 1.0 %, $p<.05$ vs. 1 hr levels), and HCN1 protein levels had also declined to 54 ± 10 % ($p<.01$), while HCN1 mRNA levels remained unchanged (110 ± 22%). We then replicated the rapid loss of I_h with an in vitro model of SE. Hippocampal slices from naïve rats were perfused with solution containing 0 Mg^{2+}, 50 iM bicuculline, and stimulation (5 stimuli at 50

Hz) of the perforant path to CA1 every two minutes for 1 hr, which produced electrographic seizure-like events recorded extracellularly in str. pyramidale. After 1 hr of this in vitro SE, dendritic I_h declined to 56 ± 13% of control ($p<.05$) , similar to that seen with in vivo SE.

Conclusions: These results demonstrate rapid loss of dendritic I_h, occurring within 1 hr post-SE, elicited by SE both in vivo and in vitro, and persisting during chronic epilepsy. Following in vivo SE, there is a delayed loss of HCN1 protein expression beginning at 1 day, while loss of HCN1 transcription is not seen until 3 days post-SE. This shows that dendritic HCN channelopathy begins at the earliest timepoints following SE, and that the early loss of I_h and HCN1 protein expression precedes the downregulation of HCN1 gene transcription, thus may be due to post-translational mechanisms.

1.039

FOCAL STATUS EPILEPTICUS IN THE SOMATOSENSORY CORTEX ENHANCES INTRINSIC EXCITABILITY AND SYNAPTIC EXCITATION IN THE RETICULAR THALAMIC NUCLEUS

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Rationale: Thalamocortical circuits are key for the generation of both partial and generalized epileptic seizures. GABAergic neurons from the reticular thalamic nucleus (nRt) inhibit thalamocortical relay cells (TCR), regulate thalamocortical transmission, and generate cerebral rhythms including those involved in thalamocortical epilepsies. nRt neurons receive excitatory inputs from both corticothalamic and thalamocortical axons and would thus receive strong excitatory input during focal and generalized seizures. The response of nRt neurons to such input is not well understood and could promote reorganization of thalamocortical circuits in ways that may lead to hyperexcitability. We therefore examined possible functional alterations in nRt neurons following prolonged episodes of acute seizure activity in the somatosensory cortex.

Methods: Focal status epilepticus (SE) was induced in male P22 mice by unilateral application of a 2 mm pledget of Gelfoam, soaked in 100 iM GABAzine, to the dura over the somatosensory cortex. Resultant focal electrographic epileptiform activity and associated contralateral partial seizures were monitored for two hours. Mice were then re-anesthetized, the incision reopened, the GABAzine pledget removed and the cortex thoroughly washed with sterile saline. The scalp was then re-sutured and animals allowed to recover. 5-7 days later whole-cell patch-clamp recordings of nRt neurons were obtained from in vitro horizontal brain slices using standard techniques in the presence of inhibitory neurotransmission blockers. Extracellular stimuli delivered to the internal capsule via a concentric bipolar electrode were used to evoke excitatory currents (eEPSCs) in nRt cells, mimicking the excitatory input from the cortex or dorsal thalamus.

Results: Two hour episodes of focal SE lead to robust and long-lasting increases in intrinsic excitability and synaptic excitation in nRt neurons. Compared to naïve controls, nRt neurons in post-status animals showed (1) enhanced post-inhibitory rebound of excitation characterized by a 2-fold increased number of rebound action potentials and a 3-fold increased duration of rebound firing; (2) increased amplitude and lowered threshold for EPSCs evoked by minimal stimulation of internal capsular axons.

Conclusions: Neocortical focal SE chronically enhances both intrinsic excitability and synaptic excitation of nRt neurons. The resultant powerful increase in inhibitory drive from nRt onto TCR cells might suppress excitatory feedback from thalamus to cortex. However, because the output of nRt neurons controls oscillations in the thalamocortical circuits, the increased GABAergic transmission from nRt to TCR cells following SE might promote abnormal oscillations in thalamocortical circuits, leading to amplification and enhanced propagation of cortical epileptic activity. Future experiments will be required to determine if the SE-induced alterations in nRt translate into enhanced thalamocortical oscillatory and epileptiform activity.

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1.045

A PUTATIVE CELLULAR MECHANISM FOR CHILDHOOD ABSENCE EPILEPSY IN PATIENTS WITH CAV3.2 GAIN-OF-FUNCTION MUTATIONS

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Rationale: Mutations of CACNA1H were discovered in patients with childhood absence epilepsy (CAE). In vitro, the mutations increase T-type Ca2+ channel activity by altering trafficking and voltage gating. Yet, the in vivo effects on seizure susceptibility and neural circuit function remain undefined. We created transgenic mice with a full length CACNA1H gene carrying either of two epilepsy-associated mutations (V831M and C456S) and a C-terminal flag tag to characterize their effects on native T-type Ca2+ currents, circuit properties, and seizure risk during postnatal development.

Methods: Spontaneous and induced seizures were measured by EEG and behavior at baseline and following i.p. bicarbonate and quantified as reported (Zhou et al. Nature Medicine 2009). Whole cell patch-clamp of hippocampal subiculum pyramidal neurons was performed in voltage-clamp and current-clamp mode in transverse hippocampal (300 ìm) slices.

Results: T-type Ca2+ currents were recorded by stepping from a holding potential of -100 mV to a set of test potentials. As reported for Cav3.2 cDNA in vitro, T-type Ca2+ currents in transgenic mice displayed a left shifted voltage-dependent activation curve relative to controls (-43±1 vs. -36±1 mV, $p<0.001$). Interestingly, T-type Ca2+ current density increased during the period of postnatal circuit developmental. At P8-10, current density in C456S mutant mice and wild type mice was not significantly different (4.6±0.4 vs. 4.5±0.4 pA/pF). However, by P17-19, current density increased and was magnified increase in mutant (8.0±0.6 vs. 5.6±0.3 pA/pF, $P < 0.01$). By contrast, in P17-19 Cav3.2 knockout neurons, current density remained low 4.6±1.1 pA/pF significantly lower than mutant at P17-19 ($P < 0.05$). The probability of firing in response to a brief (5 ms) EPSC-like stimulus of 500 pA was 100% in C456S ($n = 4$) compared to only 33% in wild-type ($n = 3$). A more prolong 1 sec current injection elicited firing at a lower threshold in C456S compared to wild type (27.3± 3.0 vs. 55.6± 8.0 pA, $P < 0.01$). Surprisingly, at P17-19, C456S mutant neurons displayed spontaneous firing at baseline: 86% in C456S mutant ($n = 7$ cells), but only 14% in wild-type ($n = 7$ cells), while resting membrane potential was unaffected (-67±1.3 vs. -67.1±0.9 mV, respectively). Hyperventilation triggers cortical spike-wave discharge in CAE patients with Cav3.2 mutations. Sodium bicarbonate injections (to induced a metabolic alkalosis mimicking the respiratory alkalosis; increasing HCO3-/CO2 ratio) epileptiform activity in frontal cortex selectively in C456S mutant mice 75% (12/16) compare to 0% of control littermates (0/12).

Conclusions: The results indicate CAE-associated Cav3.2 mutant increases T-type Ca2+ current during postnatal development to promote spontaneous discharge of pyramidal neurons and suggest childhood absence epilepsy may arise in part from a transient increase of T-type Ca2+ channels during early childhood that increases circuit excitability to promote epileptiform discharge.

1.060

PERMANENTLY IMPAIRED MITOCHONDRIAL REDOX STATUS AND OXIDATIVE/NITROSATIVE STRESS DURING EPILEPTOGENESIS

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Rationale: Reactive oxygen and nitrogen species (ROS/RNS) are mediators of oxidative stress but also function as second messengers in redox signaling. Mitochondrial dysfunction and oxidative stress are consequences of seizure activity but their contributing role to epileptogenesis is largely unknown. The goal of this study was to determine the extent of mitochondrial and tissue redox status and indices of oxidative and nitrosative stress during chemoconvulsant-induced epileptogenesis.

Methods: Adult Sprague-Dawley rats were injected with vehicle, kainate or lithium and pilocarpine and chronically monitored with video and EEG for seizure activity for up to 12 weeks. Evidence of altered redox status and reactive species production and damage was measured at different time points during epileptogenesis i.e. shortly after induction of status epilepticus, prior to development of epilepsy (i.e. seizure-free latent period), and during the chronic stages of epilepsy.

Results: In the lithium-pilocarpine model a time-dependent increase in hydrogen peroxide (H_2O_2) production that coincided with increased mitochondrial DNA (mtDNA) lesion frequency in the hippocampus was observed during epileptogenesis. In the kainate model a 20-25% increase in nitrite levels was observed shortly after treatment (8h-48h) and the 3-nitrotyrosine/tyrosine ratio increased 2-10-fold throughout all stages of epileptogenesis in the kainate and lithium-pilocarpine models. The mitochondrial redox status measured by reduced coenzyme A and its disulfide with glutathione (CoASH/CoASSG) was decreased 70-80% shortly after kainate and lithium-pilocarpine treatment and remained permanently decreased at all chronic time points. Hippocampal tissue redox status measured by glutathione (GSH) and its disulfide, GSSG, was decreased approximately 60% and remained permanently decreased throughout epileptogenesis in both the kainate and lithium-pilocarpine models.

Conclusions: The production of ROS/RNS during the "latent period" and acute and chronic phases of epileptogenesis and a permanent alteration of mitochondrial and tissue redox status in two independent animal models of temporal lobe epilepsy suggest that redox-dependent processes may contribute to the progression of epileptogenesis.

1.317A

NEUROPROTECTIVE EFFECT IN RAT HIPPOCAMPUS OF CYCLOOXYGENASE-2 INHIBITOR AND DIAZEPAM AFTER PILOCARPINE-INDUCED STATUS EPILEPTICUS

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Rationale: Status epilepticus (SE) leads to significant mortality and morbidity, and thus new neuroprotective strategies are needed. Diazepam belongs to the first line of therapeutic strategies in SE and is neuroprotective when administered at high doses within 2 h after induction of SE. Cyclooxygenase-2 (COX-2) is an inflammatory enzyme that is induced by epileptic seizures and is associated with neuronal death. The rat model of pilocarpine-induced SE was used to determine if a low dose of diazepam and COX-2 inhibitor (NS-398), when administered together, would decrease the severity of SE and reduce neuronal injury.

Methods: Electroencephalogram (EEG) electrodes were implanted in 25 male Sprague-Dawley rats. SE was induced with lithium-pilocarpine, and continuous EEG and video monitoring were performed for 24 h. Diazepam (10 mg/kg, n = 8), diazepam and NS-398 (10 mg/kg, n = 8), or vehicle (0.5% methylcellulose, n = 9) were injected at 30 min after the first motor seizure. Diazepam and control groups received vehicle 6 h later, while the diazepam+NS-398 group received NS-398. The severity of SE, evaluated as EEG power in the ã-band, was analyzed using an automated algorithm. FluoroJade B staining in the dorsal hippocampus at 24 h after SE was analyzed semi-quantitatively in CA1, CA3 and hilus of the dentate gyrus.

Results: Analysis of the electrographic data showed no difference between the control, diazepam and diazepam+NS-398 groups; severity of electrographic SE in the ã-band was similar in the three groups. Diazepam, at 10 mg/kg, did not have significant neuroprotective effect when injected at 30 min from first motor seizure. In rats treated with diazepam+NS-398, compared to vehicle rats, neuroprotection was significant in CA1 (61±3%), CA3 (63±6%) and hilus of the dentate gyrus (60±12%), ANOVA followed by Dunnet's test, $p<0.05$. Compared to diazepam alone, the combination of diazepam and NS-398 led to significant neuroprotection in CA3 (57±5%) and hilus of the dentate gyrus (55±10%), $p<0.05$.

Conclusions: We previously reported that the COX-2 inhibitor, when administered alone, decreased neuronal damage in the hippocampus (CA3: 27±4% and hilus of the dentate gyrus: 27±3%) without a detectable effect on the seizure activity associated with SE. The present data suggest that the combination of low-dose diazepam (10 mg/kg) with NS-398 leads to more effective neuroprotection in the hippocampus than NS-398 alone, and this occurs without an effect on the electrical activity during SE.

1.360

MOTIVATIONAL EFFECTS ON EXECUTIVE FUNCTION IN PEDIATRIC EPILEPSY: AN FMRI AND DTI STUDY

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Rationale: Pediatric epilepsy is associated with compromised quality of life due to behavioral limitations including executive function and motivation. We probed the integrity of the neural systems underlying executive function and reward processing in pediatric epilepsy.

Methods: Seventeen non-lesional, medically treated pediatric epilepsy patients 8-17 years of age (mean age 13 years, mean duration of

epilepsy 3 years) and individually age and gender-matched healthy community controls completed whole brain functional MRI (fMRI). During fMRI subjects performed a monetary incentive-mediated antisaccade task of response inhibition using an event related design. A cue preceding antisaccade trials indicated if subjects could win points towards a monetary reward or if the trial did not involve a monetary incentive (neutral). Participants completed 4 fMRI runs and activation from correct trials was analyzed for group differences using multivariate analyses. Diffusion tensor imaging (DTI, 6 diffusion gradient orientations with 14 sequential averages, b0=800 s/mm2) scanning was completed by a similar group of 27 epilepsy patients (mean age 13 years, mean duration of epilepsy 3 years) and 88 age approximated controls at 3T. DTI analysis used tract based spatial statistics to localize regions of compromised white matter (lower fractional anisotropy) in patients compared to controls.

Results: In the fMRI task, both groups demonstrated improved inhibitory control during reward vs. neutral conditions. However, patients made more inhibitory errors compared to controls. A widely distributed region known to support inhibitory oculomotor control and reward processing was similarly evident in both groups including visual cortex, superior parietal cortex, and orbital frontal cortex. However, patients demonstrated significantly less activation in the middle frontal gyrus, a putative cognitive control region. Higher activation in the middle frontal gyrus was associated with better antisaccade performance in the control group. DTI results showed broadly distributed regions of lower fractional anisotropy in association tracts (uncinate, superior longitudinal fasciculus), projection tracts (anterior thalamic radiations, internal capsule, and cortical spinal tract), and interhemispheric tracts (anterior and posterior corpus callosum) in the patients compared to controls. Patients had lower fractional anisotropy in the internal capsule, an important prefrontal-striatal connection in association with lower fMRI activation in the middle frontal gyrus compared to the controls.

Conclusions: Pediatric epilepsy is associated with poorer inhibitory control. While motivational effects may improve cognitive performance, patients demonstrate persistent cognitive limitations which may be associated with poorer prefrontal cortex recruitment and compromised white matter integrity in prefrontal-striatal tracts. Structural and functional brain correlates of cognitive comorbidity may have long term implications for developmental outcome in pediatric epilepsy.

3.006

LONG-LASTING ALTERATIONS IN NKCC1 AND KCC2 EXPRESSION INDUCED BY EVOKED AND SPONTANEOUS SEIZURES IN KINDLED EPILEPTIC RATS

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Rationale: GABAA inhibition powerfully controls emergent properties such as recurrent excitation and network synchronization, and is mediated by a Cl” conductance whose direction and functional effects depend on the Cl” gradient maintained by the electroneutral ion co-transporters NKCC1 and KCC2, which are driven by cation gradients generated by Na+-K+ ATPases and alter [Cl-]i without net movement of charge across the membrane. NKCC1 inwardly transports Cl- and contributes to [Cl”]i in immature neurons, while KCC2 extrudes Cl- and contributes to the transition from depolarizing to hyperpolarizing GABA responses in maturing postnatal neurons. Given the importance of the Cl” gradient for GABAA inhibition and network excitability, it was of interest to determine if repeated seizures that define epilepsy and the progression of seizures and permanent network alterations induced by brief repeated seizures evoked by kindling alter expression of NKCC1 and KCC2. Western blotting and immunohistochemistry were used to quantify expression of NKCC1 and KCC2 in the hippocampus of kindled adult rats that experienced partial seizures (Class I-IV), 3-75 evoked secondary generalized (Class V) seizures, or spontaneous Class V seizures.

Methods: Conventional western blot and immunohistochemical methods with antibodies to NKCC1 (T4 mouse monoclonal antihuman colonic T84 epithelial Na+-K+-Cl- co-transporter) or KCC2 (rabbit polyclonal anti-K+-Cl- cotransporter) were used to assess expression in hippocampal extracts and brain sections at ~24hrs or > 3 months after the last evoked seizure.

Results: NKCC1 expression increased in rats after induction of Class V seizures compared to control animals without seizures (p d” 0.05)or rats experiencing only partial seizures (Class I-IV), and increased to a maximum at ~75 Class V seizures. There were no further increases after >100 Class V seizures, a kindling stage associated with spontaneous seizures. Seizure-induced increases in NKCC1 expression were long-lasting and were noted as long as 3 months after 23-27 evoked Class V seizures. In contrast, KCC2 expression was not increased compared to controls except for a modest increase after 100 Class V seizures (pd” 0.05). Immunohistochemical analysis revealed regional alterations of expression in the hippocampal subfields and the dentate gyrus.

Conclusions: Repeated evoked secondary generalized seizures but not partial seizures induced robust long-lasting increases in expression of NKCC1 followed by modest increases in KCC2 expression at kindling stages associated with spontaneous seizures. The functional effects of the long-lasting chronic increase in NKCC1 prior to emergence of spontaneous seizures include Cl” loading that could influence E(Cl-), E(ipsp), or E(GABAa)as well as activity-dependent alterations in trans-membrane ionic gradients contributing to network synchronization and progressive adverse consequences of repeated seizures.

3.018

MINOCYCLINE AMELIORATES CEREBRAL LESIONS BUT NOT DECREASES SPONTANEOUS RECURRENT SEIZURES AFTER PILOCARPINE-INDUCED STATUS EPILEPTICUS

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Rationale: Minocycline (MINO) is a broad spectrum tetracycline derived antibiotic with anti-inflammatory properties. It has been shown that MINO could be used as a neuroprotective agent for the treatment of neurological diseases. We examined whether a single dose of MINO administered 2 h after pilocarpine-induced Status Epilepticus (SE) could diminish cerebral lesion and spontaneous recurrent seizures (SRS).

Methods: Adult Sprague Dawley rats were treated with methylscopolamine (2 mg/kg) 30 min before pilocarpine (320 mg/kg) or saline i.p. injection (Control group). All rats were treated with diazepam (10 mg/kg) i.p. 90 min after SE onset. At 20 min after diazepam injection, rats received MINO 25 mg/kg i.p. (SE+Mino group) or saline (SE group). In order to verify cerebral lesions a group of rats were transcardially perfused 5 days after SE induction. Brain sections were processed with Nissl and neuronal nuclei marker (NeuN). The number of NeuN positive cells was estimated using stereology in the piriform cortex (PC). For SRS assessment, rats were video-recorded

for approximately 5h per day, beginning 1 week after SE until 30 days later.

Results: Nissl stained sections showed that in SE rats, layer 2 was almost completely ablated in the central and posterior portions of the PC when compared to Control and SE+Mino. Quantification of NeuN labeled cells showed a large neuronal loss in SE rats (n=4; 34,882 ± 5,072; $p<0.05$) compared to Controls (n=4; 96,458 ± 3,057) that was partially recovered in SE+Mino rats (n=4; 54,015 ± 17,920; $p>0.05$). The neuron loss was more robust in layer 2 of the central PC in SE rats (19,734 ± 3,166; $p<0.01$) compared to Controls (64,843 ± 1,554) and this loss was ameliorated in the SE+Mino rats (35,125 ± 12,664). The SE rats presented a decrease of layer 2 volume (0.39 ± 0.05 mm3; $p<0.05$) compared to Controls (0.59 ± 0.05 mm3), that was partially ameliorated by MINO (0.44 ± 0.05 mm3). The analysis of SRS in rats (stage 3 or greater) showed that both SE groups (saline or Mino) presented similar SRS frequency (SE, n=6: 1,15 ± 0,19 SRS/day; SE+Mino, n=5: 1,56 ± 0,33 SRS/day; $p>0.05$).

Conclusions: These results show that MINO administered at a clinically relevant timepoint after SE proved to be neuroprotective, ameliorating neuron loss in the PC, especially in its central portion, a region known to have important influence on seizure development. However, MINO treatment did not prevent the SRS occurrence indicating that it did not prevent epileptogenic progression. Together these data indicate MINO as a neuroprotective drug but higher doses should be tested in order to achieve therapeutic effects.

3.021

HUMANIZED MOUSE MODELS OF EPILEPSY

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Rationale: Mutations in voltage-gated sodium channels have been implicated in several types of human epilepsy with varying degrees of clinical severity. Mutations in *SCN1A* were first identified in Generalized Epilepsy with Febrile Seizures Plus (GEFS+), a benign, childhood-onset syndrome in which family members have febrile seizures in childhood and may go on to develop other seizure types as adults. *SCN1A* mutations have also been identified in Dravet Syndrome (Severe Myoclonic Epilepsy of Infancy), an infant-onset syndrome characterized by generalized tonic-clonic or hemiclonic seizures. As the syndrome progresses patients develop other seizure types including myoclonic, absence and partial seizures, and a decline of psychomotor and mental development. More than 700 mutations of *SCN1A* have been reported in patients with epilepsy, making it the most common genetic cause of epilepsy. Functional studies of *SCN1A* mutations in heterologous expression systems have revealed a variety of functional defects. However, there is not an obvious correlation between Nav1.1 dysfunction and severity of the clinical phenotype. The lack of a clear genotype-phenotype correlation may reflect a limitation of *in vitro* expression systems to evaluate neuronal sodium channel mutations. The most reliable data on functional consequences of mutations can be obtained from mice engineered to carry the mutations. However, the resources and time required for generating allelic series of knock-in mice by homologous recombination is prohibitive.

Methods: Recombination-mediated cassette exchange (RMCE) allows for rapid and efficient production of an allele series of mice carrying mutant DNAs at the target locus. In this method, a cassette acceptor containing a selectable marker flanked by lox sites is targeted to the endogenous mouse locus by homologous recombination. Subsequent exchange of the cassette acceptor for the sequence of interest occurs by cre-mediated recombination in the ES cells, which is much more efficient than homologous recombination. The gain in efficiency decreases the time and resources required to generate multiple variants, allowing for parallel generation of an allelic series of mice.

Results: We generated a mouse ES cell line in which *Scn1a* exon 1 containing the translation start site was replaced by a loxed cassette acceptor via homologous recombination. Subsequent exchange with *SCN1A* cDNAs allows expression of the human cDNA under the endogenous regulatory control while ablating expression of the mouse gene.

Conclusions: This approach will enable *in vivo* characterization of human epilepsy mutations and provides a valuable resource for understanding the mechanisms underlying epilepsy and developing novel therapeutic strategies.

3.164A

INCREASED CROSSING OF CORTICO-STRIATAL CONNECTIONS FOLLOWING RESECTIVE EPILEPSY SURGERY IN CHILDREN: A PROBABILISTIC DTI TRACTOGRAPHIC STUDY

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Rationale: In Krynauw's original description (1950) on hemispherectomy for intractable epilepsy, he stated that the hemiparesis/hemiplegia is much more severe if the basal ganglia were also removed. Our own studies using PET scanning have shown that following large cortical resections in children with intractable epilepsy, robust functional changes occur in the striatum on the side of resection (Chugani & Jacobs, 1994; Chugani et al., 2008), presumably related to plasticity mechanisms. We have suggested that these metabolic changes may be due to increased cortico-striatal projections from the contralateral hemisphere to the ipsilateral striatum. In the present study, we used diffusion tensor imaging (DTI) and probabilistic tractography to test this hypothesis.

Methods: We analyzed postsurgical DTI scans from 8 children (age: 8 ± 4.3 years) with intractable epilepsy who had undergone left-sided cortical resection (anatomical hemispherectomy: 4; subtotal hemispherectomy: 2; fronto-temporal resection: 2) and compared these scans with those from 14 normal controls (age: 7.6 ± 3.1 years). All 8 patients had normal pre-surgical MRI and FDG PET findings in the right hemisphere and became seizure free after surgery. In each child, regions were manually drawn on the left caudate using the structural MRI and used as a seed region for probabilistic tractography (FSL 4.1, Oxford, UK) applying the 'two crossing fibers per voxel' model and 10,000 samples per seed voxel. The mean connectivity values were calculated for 5 contralateral cortical regions (frontal, parietal, temporal, occipital and insular cortex).

Results: Repeated measures ANOVA showed a significant interaction between the 2 groups and the 5 contralateral cortical regions ($F = 2.8$; $p = 0.05$). More specifically, the mean connectivity values between the left caudate and right frontal cortex (57 +/- 21 vs. 17.8+/-16; $p = 0.1$) and insula (1.5 +/- 0.3 vs. 0.47 +/- 0.28; $p = 0.032$) showed an apparent increase in the postsurgical group compared to controls. Whereas connectivity values between left caudate and right parietal cortex showed a decrease (0.95 +/- 1 vs. 4.3 +/- 1; $p = 0.037$), the occipital (0.44 +/- 0.2 vs. 0.83 +/- 0.16; $p = 0.16$) and temporal cortex (1.3 +/-

0.4 vs. 1.7 +/- 0.33; p = 0.54) showed no difference in connectivity between postsurgical and control groups.

Conclusions: The specific increase in fiber connectivity between caudate ipsilateral to the resection and contralateral frontal cortex and insula is consistent with our previous findings of functional changes in striatum following resection and supports the notion that, following large cortical resections, the ipsilateral caudate participates in functional reorganization. However, since preoperative DTI scans were not available in this cohort, we cannot exclude the possibility that these connectivity changes were the consequence of the left-sided lesion itself and were already present prior to surgery. This issue will be further elaborated in future studies.

3.164B

MU OPIOID RECEPTOR MRNA EXPRESSION, BINDING AND FUNCTIONAL COUPLING TO G-PROTEINS IN HUMAN EPILEPTIC HIPPOCAMPUS

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Rationale: The main goal of the present study was to characterize the mRNA expression, binding and G protein activation mediated by mu opioid receptors (MOR) in epileptic hippocampus of patients with pharmacoresistant temporal lobe epilepsy (TLE).

Methods: Epileptic hippocampal tissue was obtained from patients with intractable mesial TLE history. Epileptic patients had “en block” anterior lobectomy, ipsilateral to the epileptic focus at least 48 h after the last seizure. During the surgical procedure, hippocampal biopsies were collected immediately upon resection and quickly frozen in pulverized dry ice. Hippocampus obtained at autopsy from subjects with no evidence of neurological disease was used as controls. The human hippocampus tissue was used to evaluate MOR and GAPDH mRNA expression, saturation binding and 35S-GTPãS functional assays.

Results: In contrast with autopsy samples, hippocampus obtained from patients with epilepsy demonstrated enhanced MOR mRNA expression (116%). Saturation binding experiments revealed that the Bmax value from the epilepsy group was significantly higher (60%) when compared with autopsy samples, whereas the Kd values from both groups were not statistically different. DAMGO-stimulated 35S-GTPãS binding values from epilepsy group did not demonstrate significant alterations when they were compared with values obtained from autopsies of subjects with similar range of age. However, epileptic group demonstrated high levels of basal binding for the G proteins (136%).

Conclusions: In conclusion, our present data provide strong evidence that the epileptic hippocampus of patients with TLE presents significant alterations in MOR mRNA, binding and signal transduction mechanisms downstream of these receptors. Alternatively, such changes may represent adaptive mechanisms to compensate for other as yet unknown alterations.

3.316

CONCORDANCE OF SEIZURE SEMIOLOGY AND PHARMACOSENSITIVITY IN SIBLING PAIRS FROM THE EPILEPSY PHENOME/GENOME PROJECT (EPGP)

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Rationale: Systematic phenotype definition in the epilepsies can help direct the search for susceptibility genes. Prior studies have identified distinct genetic effects on localization related (LRE) vs. generalized epilepsy (GE), myoclonic vs. absence seizures, and the generalized tonic-clonic seizure types within the idiopathic generalized epilepsies (IGEs). Here, we examine the genetic effects on specific seizure semiology within LREs, and on pharmacosensitivity (PS) to antiepileptic drugs (AEDs).

Methods: We examined seizure semiology and pharmacosensitivity (PS) in sibling pairs from EPGP, a multicenter collaborative consortium that collects in-depth phenotype and genotype data from a large number of patients with epilepsy to investigate the genetic influences on common and rare forms of epilepsy and pharmacosensitivity. We completed seizure symptom data on 102 sibling pairs with IGE and/or LRE. 51 of these pairs are concordant for IGE, 31 are concordant for LRE, and 20 are discordant (one sibling has IGE, the other LRE). Within the 31 pairs concordant for LRE, we examined concordance of focal seizure symptoms in the following categories: aphasia, autonomic, psychic, sensory, and motor. We also examined the concordance of PS within 20 sibling pairs in which both siblings were definitively classified according to PS. The analytic approach fit a logistic regression model in which presence of a symptom category in the proband was the predictor of presence of the same category in the sibling. Under the null hypothesis of no familial aggregation of symptom types, there should be no association between proband and sibling. The extent to which the estimated log-odds differs from zero was used to test for association.

Results: Probands and siblings were significantly associated for aphasic (1-sided p-value=0.003), autonomic (0.04), psychic (0.012), and sensory (0.004) symptom categories. The sibpair association for motor symptoms was suggestive (p=.074). The results of analysis of pharmacosensitivity data were suggestive of sibling concordance, though numbers were too small for statistical significance. Among siblings of probands who were PS (N=12), all were also PS, whereas among siblings of probands who were not PS (N=8), 6/8 were PS (p=0.15).

Conclusions: Analysis of focal seizure symptom concordance in EPGP sibling pairs provides evidence for distinct genetic effects on aphasic, autonomic, sensory, and possibly motor symptoms. This evidence can help clarify the role of genes in determining the specific manifestations of the epilepsies, and may allow a priori identification of disease subtypes that are more likely to share susceptibility genes within the focal epilepsies. Analysis of PS data in sibling pairs suggests that there may be a genetic effect on pharmacosensitivity. As enrollment and data collection proceeds in EPGP, analyses using larger numbers of subjects will better address this question, and will allow stratification of PS by epilepsy type.

3.341

NRSF / REST DEPENDENT AND INDEPENDENT GENE PATHWAYS IN EPILEPTOGENESIS

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Rationale: A number of receptors (e.g., GluR2), ion channels (e.g., HCN1) and transporters (e.g., Kcc2) regulated by the transcriptional repressor NRSF have recently been found to be altered in the epileptic hippocampus. This suggests that repression by NRSF may define a general mechanism by which expression of gene clusters crucial to normal neuronal function might be deranged after insults that promote hyperexcitability and spontaneous seizures.

Methods: Genome-wide expression analysis was performed using Illumina RatRef-12 Expression Beadchips. Experimental groups included controls and rats that experienced kainic-acid-induced status epilepticus (KA-SE). Control and KA-SE groups were treated with oligodeoxynucleotides (ODNs) comprising either the NRSE sequence (as a 'decoy' preventing NRSF binding to its cognate DNA-binding sequence) or a scrambled sequence. In all cases, the CA1 region of the hippocampus was resected two days after KA-SE and mRNA recovered.

Results: 470 genes were repressed by kainic-acid-induced status epilepticus (KA-SE). Of these, 39 contained an NRSE, including, KCC2, TAP1, Kv3.2, NELL1, Grik5, GluR2, NMDA receptor type 2A, SCN3B, GLRA2, KCNIP2, and HCN1. In total 49 ion channels were reduced, of which 22 have a functional NRSE. Treatment with NRSE ODNs left 347 genes repressed, but only 2% contain putative NRSE binding sites. Pathway and cluster analyses showed that ion channels were commonly reduced by KA-SE and rescued by the ODNs. Another major cluster of these NRSF dependent genes is that of calcium binding proteins. NRSF independent gene changes were manifest after KA-SE. These included gene clusters related to stress response and inflammation. Functionally, administration of NRSE ODNs to KA-SE attenuated subsequent hippocampal hyperexcitability and the severity of the resulting epilepsy.

Conclusions: (1) NRSF dependent and independent changes in the expression of gene clusters are provoked by insults resulting in epilepsy.

(2) Rescue from repression, using NRSE ODNs is relatively selective for NRSE-containing genes.

(3) This rescue attenuated the conversion of the hippocampal network into a hyperexcitable one, and the generation of epilepsy, suggesting that NRSF might be a 'master switch' in the coordinated program that promotes hyperexcitability after KA-SE and similar insults.

Therefore, the selective suppression of the function of specific transcription factors, followed by genome-wide analysis provides a powerful tool to uncover genes that are crucial for epileptogenesis and might be therapeutic or preventive targets.

3.362

MTOR CASCADE ACTIVATION OBSERVED IN HUMAN HIPPOCAMPAL SCLEROSIS IS NOT RECAPITULATED IN A RAT PILOCARPINE MODEL OF EPILEPSY

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Rationale: Previously we have shown that scar astrocytes found in hippocampal sclerosis (HS) in MTLE revealed increased phosphorylation of ribosomal protein S6 (pS6) (Mikell et al., 2009). In order to elucidate mechanisms of mTOR cascade activation in HS, we studied mTOR cascade in the development of the gliotic scar emerging after neuronal loss in a pilocarpine model of epilepsy in rats.

Methods: We used immunohistochemistry and western blotting to evaluate levels of phosphorylated and non-phosphorylated downstream components of mTOR, p70 S6K, S6 and 4EB-P1, in a pilocarpine-induced model of epilepsy in rats and in surgically resected hippocampi in patients with medically intractable MTLE.

Results: Two brain areas in pilocarpine treated rats usually revealed severe neuronal damage and accompanying astrogliosis: hippocampus and piriform/entorhinal cortex. In the first two weeks after insult, reactive astrocytes bordering the damaged areas expressed high levels of pS6. In one month after insult, only a few astrocytes bordering this area were pS6 immunopositive. Later on, when the glial scar began to form, gliotic astrocytes did not show activation of mTOR pathway. Thus in 3, 6 months and in 1.2 years (the latest time studied) scar astrocytes did not show mTOR activation and only some neurons were pS6 immunopositive. In all studied cases of human HS, scar astrocytes revealed high levels of pS6 and 4EB-P1.

Conclusions: Based on the known data about the kinetics of mTOR activation, we argue that HS in surgically resected cases of MTLE is not a static phenomenon finalizing neuronal demise. In contrast to the traditional gliotic scar, in HS, there are some ongoing cellular processes that result in mTOR pathway activity.

3.365

IMMATURE LARGE NEWBORN NEURONS IN HUMAN HIPPOCAMPAL DENTATE GYRUS FROM PATIENTS WITH TEMPORAL LOBE EPILEPSY

Hidenori Sugano, M. Nakajima, H. Okura, T. Higo and H. Arai (Juntendo University, School of Medicine, Tokyo, Japan)

Rationale: The aim of this study is to evaluate the maturation of the newborn neuron in the hippocampal dentate gyrus using human specimens from the patients with temporal lobe epilepsy.

Methods: Human hippocampal specimens were obtained at surgery for temporal lobe epilepsy and divided into two groups: with or without hippocampal sclerosis (HS). We stained them for newborn neurons by PSA-NCAM, and counted positive cells in the subgranular cell layer (SGCL) and hilus. We also stained for Hu, Doublecortine (DCX), NeuroD, NeuN with PSA-NCAM to analyze the maturation of these newborn neurons. We also used NKCC1 and KCC2 stains to demonstrate the maturation of ion-transporters.

Results: More PSA-NCAM positive neurons were seen in the group without HS than with HS. Size of the newborn neurons in the group without HS was the same as the mature granular cell. However, 38.4% out of all newborn neurons in the HS group were large cells more than 30im. From the large newborn neurons population, 79.5% were located in the hilus, and more than 80% stained with Hu, NeuroD, and NeuN. The percentages of DCX and KCC2 positive large neurons in the group with HS were less than those of the group without HS. The percentages of NeuroD, DCX, NKCC1, and KCC2 positive small newborn neurons in the hilus in the group with HS were less than those without HS. In the group without HS, NeuroD and NKCC1 positive newborn neurons in the SGCL were reduced in number.

Conclusions: The large newborn neurons in the hilus are immature, and the maturation of those cells continues with their migration to SGCL and reduction of cell size. In the group with HS, few mature newborn neurons were located in the SGCL and the neuronal maturation was restricted.

IMAGE: images/903442_A.jpg

IMAGE: images/903442_B.jpg

Sunday, December 5, 2010

Investigators' Workshop Sunday Afternoon Session I
2:30 p.m.-4:00 p.m.

IW.09

'INTERNEURONOPATHIES' - DIVERSITY IN THE PHENOTYPES OF GENETIC MUTATIONS THAT ALTER FOREBRAIN GABAERGIC INTERNEURON ONTOGENY

Elizabeth Powell (Anatomy & Neurobiology, Univ Maryland School of Medicine, Baltimore, MD)

Summary: Disturbances in genes that control GABAergic neuronal ontogeny share a common outcome of seizure susceptibility. However, the overall anatomical characterizations are diverse, with some mutations leading to severe malformations, whereas losses of other genes have brains that appear to be largely normal. The affected subpopulations are biochemically unique. The reported onset and types of seizure behaviors varies with genetic manipulation and interneuron repertoire. This workshop will review the common developmental origins of the forebrain interneurons and compare anatomical and physiological outcomes with genetic disruptions. Where possible, strategies for correcting or repairing the deficits will be discussed.

IW.10

ADENOSINE AND EPILEPSY - PROMISING START INTO A NEW CENTURY: THE FIRST DECADE

Detlev Boison[1], Thomas H. Swanson[2], Philip Haydon[3] and Susan A. Masino[4] ([1]Robert Stone Dow Neurobiology Laboratories, Legacy Research, Portland, OR; [2]University of Montana, Missoula, MT; [3]Neuroscience, Tufts University, Boston, MA and [4]Life Sciences, Trinity College, Hartford, CT)

Summary: The focus of this workshop is recent translational research on the purine ribonucleoside adenosine, which is an endogenous anticonvulsant of the brain with demonstrated efficacy in pharmacoresistant epilepsy. Although it has been known for 30 years that endogenously released adenosine regulates excitability in the hippocampus (1), only the advent of new molecular tools within the past 10 years has spawned a new era of translational research on adenosine.

Recently, non-neuronal, in particular glial, mechanisms have received much attention for their pathogenetic role in epilepsy. Studies performed in genetically engineered mice have demonstrated that synaptic levels of adenosine, and thus hippocampal excitability, are largely regulated by astrocytes (2,3). It has further been demonstrated that astrogliosis and astrocyte dysfunction - pathogenetic hallmarks of the epileptic brain - directly affect adenosine signalling and hippocampal excitability.

Findings that adenosine dysfunction is involved in the pathogenesis of epilepsy provide a direct neurochemical rationale for therapeutic intervention. Novel polymer-, stem cell- and gene- based approaches have demonstrated that focal adenosine augmentation is an effective strategy to suppress seizures in models of epilepsy (4) and recent findings suggest that therapeutic benefits of a ketogenic diet are at least partly mediated by an adenosine-related mechanism (5).

Tom Swanson will provide a general introduction into the role of adenosine within the context of epilepsy and will provide a Clinician's perspective of this timely topic. Phil Haydon will discuss the role of astrocytes in regulating adenosine levels and seizure susceptibility. Susan Masino will conclude with novel adenosine-based therapeutic approaches that include the ketogenic diet and focal adenosine augmentation approaches.

The expected outcome of this workshop is a detailed understanding how adenosine function and dysfunction are involved in the regulation of ictogenesis and epileptogenesis and how those findings can be translated into adenosine-based therapeutic strategies.

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IW.11

DE-STANDARDIZING AED THERAPY DEVELOPMENT: TRANSLATING 'TRANSLATIONAL' RESEARCH INTO CLINICAL TRIALS

Cynthia L. Harden[1], Emilio Perucca[2], Mark Quigg[3], Jacqueline French[4] and Susan Herman[5] ([1]University of Miami, Miami, FL; [2]University of Pavia, Pavia, Italy; [3]University of Virginia, Charlottesville, VA; [4]New

York University, New York, NY and [5]Beth Israel Deaconess Medical Center, Boston, MA)

Summary: Clinical treatment trials for seizures disorders are usually consist of trying to enroll a patient population that has a high frequency of a specific seizure type, then blindly and randomly treating them with an antiseizure drug versus placebo and comparing seizure frequency before and after treatment. This study design is adequate to evaluate effectiveness to a limited extent for short-term oral medication treatment trials. However, epilepsy clinical investigators are often inspired by their patients to study other important outcomes including cognitive, behavioral and endocrine outcomes. Further, novel treatment approaches currently under development such as gamma-knife treatment for temporal lobe epilepsy and anti-inflammatory molecular interventions for intractable epilepsy require using different timelines and outcomes measures than standard antiseizure drug trials. Finally, the influence of the basic science epilepsy researchers on clinical trials in humans is enormous yet the strategies of testing hypotheses derived in the lab to human clinical trials remains unsystematic and unsatisfying for investigators on both sides of the aisle. We will provide a forum for presenting several real and several proposed clinical trial designs that incorporate novel outcome measures and are informed by basic research. There will also be discussion and critique of the trials. Clinical investigators and especially basic science investigators are encourage to attend and to participate in the discussion.

The clinical trials under discussion will include a trial of cognitive preservation in temporal lobe epilepsy, testosterone levels and behavior alterations with antiseizure drugs, the trial design of using gamma-knife to treat temporal lobe epilepsy and a proposed approach to evaluating anti-inflammatory antiseizure treatments, incorporating such considerations as an appropriate study population and biomarkers for efficacy or toxicity. The presenters will be Drs. Quigg, Perucca and Harden. The discussion leaders will be Drs. Herman and French.

Sunday, December 5, 2010

Investigators' Workshop Sunday Afternoon Session II
4:15 p.m.-5:45 p.m.

IW.12

SYNAPSE FORMATION, PRUNING AND EPILEPTOGENESIS

David A. Prince[1], Beth Stevens[2] and Cagla Eroglu[3] ([1]Neurology, Stanford University School of Medicine, Stanford, CA; [2]Neurology, Harvard Medical School, Boston, MA and [3]Biology, Duke University Medical Center, Durham, NC)

Summary: The expression of several key molecules critical for synapse formation and removal during development may be altered after injury and in CNS disease states, resulting in functionally abnormal, epileptogenic brain. Beth Stevens will discuss the role of members of the classical complement cascade, C1q and C3, and microglia in synapse elimination during development and during the early stages of neurodegenerative disease. Absence of these molecules leads to a hyper-connected brain. Cagla Eroglu will review the role of astrocyte-secreted extracellular matrix proteins, thrombospondins, in synapse formation and show that the calcium channel subunit, á2ä-1, is the receptor for both thrombospondin and the anticonvulsant and analgesic drug gabapentin. Overexpression of á2ä-1 may lead enhanced to synaptogenesis and gabapentin is a potent inhibitor of excitatory synapse formation. David Prince will describe results of experiments in genetically altered mice in which either elimination of C1q or overexpression of á2ä-1 results in epilepsy. He will present recent data suggesting that gabapentin is an effective antiepileptogenic agent after neocortical injury.

IW.13

EARLY DETECTION OF EPILEPTOGENESIS AND THE SEARCH FOR PREVENTATIVE TREATMENTS IN EXPERIMENTAL MODELS AND THE CLINIC

Anatol Bragin (Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA)

Summary: Every day about 500 people develop epilepsy as a consequence of traumatic brain injury (TBI), and 60-80% of these patients have seizures that are refractory to treatment. Up to 45% of patients with severe TBI develop epilepsy, suggesting that this patient population would be an ideal group for the testing of antiepileptogenesis treatments. However, given the risks inherent in testing drug treatments in asymptomatic patients, a major challenge is how to select those subjects with the highest likelihood of epilepsy for this early preventive treatment. Recently, new biomarkers have been identified that predict the likelihood of developing epilepsy after status epilepticus, which suggests that the opportunity to identify at-risk TBI patients may soon be a reality. Unfortunately, we currently do not have promising drugs that are effective for the prevention of epileptogenesis, nor do we have an accepted strategy for preventive treatment. During this session, Dr. Lowenstein will discuss the current situation concerning the treatment of patients with initial brain injury such as TBI, encephalitis and stroke; Dr. Jensen will review emerging information about basic mechanisms and molecular signaling cascades involved in epileptogenesis and their potential as targetable intervention points; and Dr. Karsten will present data related to the prediction of epileptogenesis after brain injury on the basis of analysis of peripheral blood samples. The discussion will focus on the practical steps that should be taken to implement earlier preventive treatment in the clinic.

Sunday, December 5, 2010

Investigators' Workshop Poster Session
6:00 p.m.-7:30 p.m.

1.001

THE RELATION BETWEEN INTERICTAL SPIKES AND SEIZURES IN RAT MODELS OF EPILEPSY

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Rationale: Interictal spikes (ISs) are biomarkers for excessive brain excitability in epilepsy. However, the relationship between IS frequency and pattern and seizure development is not well understood. In some acute seizure models, ISs increase in frequency and complexity just before seizures and appear to be the triggering event. In other epilepsy models, there appears to be little relationship. In human patients, there is a suggestion that spikes increase after seizures and then decline thereafter. If there is a relationship between seizures and ISs, it is likely to be more clearly seen in animals that exhibit clustered seizures. We hypothesize that repetitive seizures increase the frequency of ISs, and the seizure clusters or ISs slowly induce a homeostatic mechanism that may end the cluster and reduce the likelihood of subsequent seizures for days or weeks.

Methods: Status epilepticus (SE) was induced in male Sprague Dawley rats by either i.p. injection of pilocarpine (n=15) or electrical

stimulation of the perforant path bilaterally for 3 hours (n=8) or unilaterally for 8 hours (n=10). Animals that developed spontaneous recurrent seizures were continuously monitored with bilateral intracranial electrodes and video for periods up to 6 months. Automated spike and seizure detecting software were used for analysis, with video confirmation of seizures.

Results: Adult rats that undergo either chemically or electrically induced SE develop chronic epilepsy at various times after the inducing stimulus. ISs are invariably present in those animals that develop epilepsy. In animals that exhibit clustered seizures (n=8, clusters occur at 7-14 day intervals with 10-50 seizures per cluster), ISs are often at their lowest frequency before the seizure clusters, increase in frequency during the cluster (over 1-2 days), continue to increase in frequency after the seizures subside (over 1-2 days), and then slowly decline over several days to low levels before the beginning of the next cluster. In animals with only isolated seizures, a similar pattern can be observed.

Conclusions: Our data suggest that clusters of seizures are most likely to occur during periods of reduced IS firing. The seizures are associated with (or cause) an increased IS firing (especially during intense clusters) which may paradoxically reduce the likelihood of subsequent seizures. The time course of the phenomena in the rats with clustered seizures suggests that slow molecular events may be occurring that serve to both enhance some forms of brain excitability (ISs) while at the same time, reducing the tendency for subsequent seizures for substantial periods. It has been shown, for example, that repetitive seizures can induce normally glutamatergic granule cells to produce and secrete GABA and that this change in neuronal phenotype lasts for approximately one week. It is likely other homeostatic mechanisms are also involved in dampening excessive brain excitability. Identifying these mechanisms may provide new targets for innovative anti-seizure therapy.

1.006

ROLE OF TRKB RECEPTORS, AND PRESYNAPTIC AXONAL SPROUTING IN HYPEREXCITABILITY AFTER SCHAFFER COLLATERAL TRANSECTION AND ITS CONTRIBUTION TO POSTTRAUMATIC EPILEPSY

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Rationale: Posttraumatic epilepsy (PTE) is a common and serious complication of acute traumatic brain injury (TBI), especially after dural penetration. Seizures occur after a latent period of months to years. This delay in epileptic development suggests the initiation of a slow process after injury leading to a permanently epileptic brain. We have modeled a penetrating TBI by transecting the Schaffer collateral (SC) pathway in vivo and in vitro. These lesions have been shown previously to result in delayed axonal sprouting of CA3 pyramidal cells in vitro and an increase in the probability that CA3 cells are connected by excitatory synapses. The extent of this axonal sprouting is correlated with hyperexcitability and transgenic mice with reduced trkB expression are less likely to exhibit axonal sprouting after SC transection. We now extend these findings using mice in which a single amino acid mutation in the trkB receptor (F616A) has been knocked-in rendering it susceptible to pharmacological blockade by 1NMPP1 (Chen et al., 2005). TrkBF616A receptors are fully functional without the drug present and allow for full pharmacological blockade in the presence of the drug.

Methods: SC pathway transection was performed in hippocampal slice cultures derived from trkBF616A mice at day in vitro 14; cultures were treated with 1NMPP1 or normal media. Cultures were processed for immunohistochemical and Western blot (WB) analysis of GAP43, a marker for growing axons. In order to determine the contribution of trkB receptors and axonal sprouting under more physiological conditions, we performed SC transections in vivo in trkBF616A mice using a microknife mounted on a stereotaxic carrier. Extracellular recordings of acute physiology slices were carried out to determine hyperexcitability. WB analysis was carried out to determine GAP43 levels after lesion.

Results: Our in vitro model revealed that the number of GAP43 immunoreactive fibers in the vicinity of the lesion was significantly reduced in cultures treated with 1NMPP1, compared to untreated cultures. Blockade of the trkB receptor with 1NMPP1 prevented the increase in GAP43 protein levels that were observed after the lesion (n=4, p=0.001, ANOVA).Extracellular recording in area CA3 from acute hippocampal brain slices obtained the in vivo model showed a marked increase in their coastline bursting index indicating they were hyperexcitable (n=6, p=0.001, ANOVA). WB analysis of GAP43 levels indicated an increase GAP43 protein following the lesion as compared to sham controls (n=4, p=0.001, ANOVA).

Conclusions: We confirm our previous suggestion that lesion induced neurotrophin-trkB signaling is a critical promoter of axonal sprouting after injury. We are currently treating mice with 1NMPP1 to test the hypothesis further that trkB receptor activation is required for injury-induced axonal sprouting and hyperexcitability. These data will provide a better understanding of the role of trkB receptor signaling and axonal sprouting after TBI and PTE.

1.017

EARLY-LIFE SEIZURES LEAD TO INCREASED AMPA SUBUNIT-CONTAINING SYNAPSES AND HIGHER CA2+ RESPONSES IN RAT PYRAMIDAL CA1 NEURONS

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Rationale: Hypoxia is the leading cause of perinatal seizures, affecting 1-3% of infants. In rats at postnatal day (P)10, hypoxic seizures (HS) lead to increased seizure susceptibility and neurobehavioral deficits later in life, as well as hyperexcitability in hippocampal area CA1 (Jensen et al 1998) and in vivo spontaneous seizures (Rakhade et al SFN 2008). Whole-cell patch clamp recordings in CA1 neurons show a decrease in functionally silent, NMDA-receptors (NR) only containing synapses within 48hrs of HS at P10 (more AMPA receptor (AMPAR) functional synapses, Zhou et al SFN 2008). HS also downregulates GluR2 expression, increasing calcium (Ca2+) permeability in AMPARs (Koh et al 2004, Rakhade et al 2008). Here we aimed to determine 1) if we could identify the alteration in "silent synapses" morphologically, and 2) whether seizure-induced changes in synaptic AMPARs alters the functional Ca2+ response of CA1 pyramidal neurons.

Methods: Seizures in P10 rats were induced by global hypoxia. To study morphology, brain sections from P12 rats 48hrs post-HS were triple-labeled with NR subunit NR1, AMPAR subunit GluR1, and presynaptic marker synaptophysin (syn). After confocal microscopy (blinded) of CA1 s. radiatum, we counted NR1 puncta, syn puncta in contact with NR1, and GluR1 puncta in contact with NR1/syn. We used the ratio of NR1/syn-only puncta to NR1/GluR1/syn puncta to assess the % silent/total NR1 synapses. To examine Ca2+ responses

due to changes in AMPAR expression, slices from rats 48hrs post-HS were labeled with ratiometric Ca2+ indicator dye Fura-2. During wide-field time-lapse imaging, slices were stimulated with kainate (KA), then treated with 150uM n-acetyl spermine (NASP), and exposed to kainate again.

Results: At 48hrs post-HS, the ratio of NR1-only to NR1/GluR1 synapses was significantly reduced by 45% in the s. radiatum of CA1 compared to age-matched controls (4.7±2.6 post-seizure, 8.6±3.5 in controls; n=4 rats/group; p=0.003). Fura-2 imaging in the same area of CA1 in live slices from rats 48hrs post-HS, revealed that peak Ca2+ change from baseline was significantly higher in pyramidal neuron somas compared to controls after a low (2.5uM, 8% mean increase, p=0.016, n=5 rats/group) or high (50uM, 17% increase, n=6 rats/group; p=0.008) KA bath application. NASP, which specifically blocks GluR2-lacking AMPARs, diminished the increased Ca2+ response to 50uM KA in slices from post-HS rats (2% increase post-HS, p=0.25, n=3/group).

Conclusions: These results suggest that within 48hrs of neonatal seizures, AMPAR subunit incorporation increases at glutamate receptors containing NRs, corroborating our previous electrophysiology findings. Further, this results in a functional increase in Ca2+ response to stimulation with KA, consistent with our prior studies showing reduced GluR2 subunits. Together, this suggest that changes in synapse function during this critical period of synaptic development in early life may contribute to epileptogenesis and cognitive dysfunction seen in this model of neonatal seizures.

RO1NS31718, DP10D003347, F32NS068161, P30HD18655

1.038

RECURRENT SEIZURES SUPPRESS DENDRITIC GROWTH OF DEVELOPING HIPPOCAMPAL PYRAMIDAL CELLS

MASATAKA NISHIMURA and J. W. Swann (Pediatric-Neurology, Baylor College of Medicine, Houston, TX)

Rationale: Neuronal activity is known to play an important role in dendrite development. But the impact abnormal seizure activity has on dendrite growth and maturation has rarely been studied. Previous experiments in our laboratory have shown that when hippocampal slice cultures, taken from mice 4-6 days-old, are grown in media containing bicuculline (100µM) for 1 week, dendritic growth is markedly suppressed. We have also shown that recurrent seizures suppress the molecular maturation of hippocampal glutamatergic synapses in vivo using the flurothyl model. These results motivated us to study how recurrent seizures affect dendritic growth in developmental CA1 hippocampal pyramidal cells in vivo.

Methods: Experiments were performed using Thy1-GFP-M mice obtained from Jackson Laboratory. On postnatal days (P) 7-11, brief (3 min) flurothyl-induced seizures were produced in infant mice. Three seizures were induced daily for 5 days. Sham littermate control mice were handled identically but without exposure of flurothyl. Following treatment, mice were allowed to survive for varying periods of time (1-20 days) before brains were removed for analysis. On P12, 15, 20, 25, 30, brains were fixed and 300µm slices were made. CA1 hippocampal pyramidal cells were confocally imaged and the basilar dendrites reconstructed using Neurolucida.

Results: Under control conditions, the basilar dendrites of CA1 pyramidal neurons grow rapidly during the first 2 postnatal weeks. For instance, between P6 and P15 the average length of the basilar dendrite nearly doubles from 1354 ± 85 µm to 2548 ± 133 µm (SEM). Thereafter, the dendrites continue to grow but at a reduced rate until P25-30. Sholl analysis indicates that as the hippocampal pyramidal cells mature they add branches both near (< 50 µm radial distance) and at a distance (between 50 and 250 µm) from their somas. In mice that experienced recurrent seizures between P7 and 11, the total length of basilar dendrites is reduced 15.8 % (2494 ± 147 versus 2100 ± 124 µm, $P<0.05$) at P25 and the growth is dramatically arrested from P12 (1958 ± 155 µm) to P30 (2058 ± 120 µm). Comparison of Sholl analyses of seizure-treated samples and their controls indicate that shorter dendrites predominate early-in-life (P12- P20) in experimental samples but with further maturation fewer dendrites of all lengths are observed.

Conclusions: These results suggest that the interruption of synaptic maturation and decreases in molecular markers for glutamatergic synapses seen previously in the flurothyl model may be at least in part be due to a reduction in dendritic arborization. Since dendrites undergo rapid growth during early life, recurrent seizure in vivo may retard or even arrest dendritic growth. Our results suggest that developing neural networks employ unique compensatory mechanisms to control chronic network hyperexcitability. Neuronal network abnormalities produced by the morphological changes reported here could be an explanation for the learning and memory deficits observed in numerous models of early-onset epilepsy.

1.042

PATHWAYS OF INTERICTAL SPIKE PROPAGATION ARE DETERMINED BY NETWORK INHIBITION

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Rationale: Interictal spikes (IIS) are highly correlated with the presence of seizures, and this is the basis of their use as biomarker for epilepsy. Unfortunately the mechanisms underlying IIS initiation, propagation and termination, their role in epilepsy, and the basis for correlation with seizures remain uncertain. In this study we used recordings of human epileptic networks, calcium imaging in vitro, and computational modeling to explore one of these questions, namely the origin of the variance in IIS morphology.

Methods: To study the source of IIS variance, we analyzed the initiation and spread of IIS in patients with long standing pharmaco-resistant epilepsy. We used electrocortigraphic data from subdural grids to map the propagation of IIS through cortex by stacking spatial averages of ÄV at all electrodes for each time point. To study the network determinants of IIS propagation, we used calcium imaging to map IIS-like trajectories in chronically epileptic hippocampal organotypic slices. We also used a large-scale computational model of the CA3 region of hippocampus based on Traub and Miles (1991) with added constraints to make the network scale-free. Connectivity between cells was random and decreased with distance . A limited number of hub-cells were strongly connected with other cells.

Results: Even for multiple spikes originating from a single location, IIS had variable onset trajectories. The recruitment of the same cortical areas occurred in a unique sequence for each spike. Calcium imaging also supported the idea that activation of different areas of the network occurred in unique sequences for each spike in individual hippocampal cultures. To test the influence of interneurons on the pattern of network activation during spikes, we blocked GABA-mediated synaptic inhibition, resulting in most of the trajectory variance being removed.

We used the computational model of CA3 hippocampal network to simulate and extend these results. With intact inhibition series of locally synchronized activity occurred randomly throughout the network, and was extinguished by GABAergic inhibition. This activity created localized refractory areas, through which subsequent large-scale synchronous activity propagated poorly, influencing future spikes locations and trajectories. After blocking inhibition, local events were no longer quenched, thus every initiation could spread to involve the entire network, and the pathway variance due to local refractory areas was lost.

Conclusions: In networks with intact GABAergic transmission, inhibition is sufficient to quench nascent IIS, leading to formation of local refractory areas. These refractory areas strongly affect propagation trajectories of subsequent IIS leading to high degree of pathway variability. On the other hand in networks with impaired inhibition the amount of quenching is decreased, resulting in low variability. Thus pathway variance could be used as a noninvasive measure of the functional integrity of the inhibitory system.

1.055

RAPAMYCIN SUPPRESSES MOSSY FIBER AND SOMATOSTATIN INTERNEURON AXON SPROUTING BUT NOT EPILEPTOGENESIS IN A MOUSE MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: Patients with temporal lobe epilepsy display many pathological changes in the dentate gyrus, including hilar neuron loss, granule cell axon (mossy fiber) sprouting, GABAergic axon sprouting, ectopic hilar granule cells, and others. It is unclear which of these circuit anomalies, if any, contribute to epileptogenesis. To address that issue, one would like to selectively block specific changes and identify those that affect development of spontaneous seizures. Recent evidence suggests the mTOR inhibitor, rapamycin, might be useful in this regard.

Methods: GIN mice, which express GFP in a subset of somatostatin interneurons, were treated with pilocarpine to induce status epilepticus. Beginning 1 d later, mice were treated daily with rapamycin (3 mg/kg, ip). To evaluate epileptogenesis, mice were video-monitored daily 9 h/d during the second month after pilocarpine-induced status epilepticus. To more rigorously evaluate epileptogenesis, mice were video-EEG monitored with an electrode implanted in the hippocampus. Recordings were obtained daily 9 h/d during the third month after status epilepticus.

Results: After 2 months, rapamycin-treated mice displayed less mossy fiber and less GFP-positive axon sprouting in the granule cell layer + molecular layer compared to vehicle-treated controls. Hilar neuron loss, number of granule cells, and number of Prox1-immunoreactive hilar ectopic granule cells was similar in rapamycin- and vehicle-treated epileptic mice. The frequency and severity of seizures was similar in rapamycin- and vehicle-treated mice.

Conclusions: One interpretation of these data is that axon sprouting in the dentate gyrus is not epileptogenic but hilar neuron loss and generation of ectopic granule cells might be. However, mossy fiber and somatostatin axon sprouting might have opposing effects, and rapamycin might affect epileptogenesis through other mechanisms that were not evaluated in the present study. Nevertheless, these findings suggest that targeting signal transduction mechanisms is a useful strategy to more selectively test the epileptogenicity of circuit changes in temporal lobe epilepsy.

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1.057

GENE PROFILING OF THE CA1 AFTER MULTIPLE EARLY-LIFE SEIZURES

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Rationale: Although early-life seizures may be harmful and increase the risk of epilepsy later in life, postnatal seizures acquired due to asphyxia or other early traumas may lead to tolerance to prepare the brain from the impact of a subsequent injury. Previously, we demonstrated that postnatal (P) P20 juvenile rats are sensitive to CA1 injury following a single injection of kainic acid (KA) (1xKA) but resistant to this damage when the animals have a history of two prior seizures on P6 and P9 (3xKA). We hypothesized that the two earlier seizures, in the neonatal period, led to neuroprotection via a pre-conditioning mechanism involving attenuation of Ca2+ currents and induction of survival signaling pathways.

Methods: The CA1 was microdissected away from the other hippocampal subregions and total RNA was extracted, subjected to RT-PCR then hybridized with a rat microarray platform to identify genes involved in the protective effects produced by multiple early-life seizures. Ca2+ influx with FURA 2-AM imaging was used to monitor glutamatergic receptor efficacy after 1xKA vs. 3xKA.

Results: Microarray results indicated that over 13,000 genes were regulated in the CA1 after a single seizure induced in the juvenile period, but also that a large percentage of them were differentially regulated if the animals had a history of two neonatal seizures. Of the total number of altered genes only 11 were commonly decreased and 389 were commonly increased. Examples of protective genes that were up-regulated after 3xKA were anti-apoptotic Bcl-2 gene members and adaptor proteins such as adaptor protein complex AP-1, sigma 1 adaptor protein, phosphotyrosine interaction, and adaptor-related protein complex 3, mu 2 subunit. Differential regulation of cytokines also favored protection. Annexins and S100 proteins two large, but distinct, calcium-binding protein families were differentially regulated; annexin 3 was increased after 3xKA but not after 1xKA. Calmodulin 2 was decreased after 1xKA but increased after 3xKA. Ca2+ imaging studies also showed that N-methyl-D-aspartate (NMDA) responses were enhanced at 5 hrs after 1xKA but these elevations were attenuated after 3xKA.

Conclusions: Described changes may contribute to early-life seizure-induced pre-conditioning and neruroprotection. This could be achieved by reduced glutamate receptor-mediated Ca2+ permeability of the hippocampus and redirecting apoptotic pathways.

1.136

PROPAGATION OF INTRACRANIAL ELECTROENCEPHALOGRAPHIC ACTIVITY BETWEEN NEOCORTEX AND SUBCORTICAL STRUCTURES AS AN INDICATOR OF SEIZURE ONSET

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Rationale: Epilepsy surgery planning can be complicated when intracranial EEG monitoring reveals ictal patterns with a broad regional neocortical onset, particularly if the onset region includes eloquent cortex. In some cases, however, a regional ictal pattern may arise from ictal activity that is propagated from other structures that might be safer to resect. This is most evident when a lesion is present in nearby neocortex or in mesial temporal structures, but may also occur in the absence of a lesion. Recordings from both intracranial depth electrodes and subdural electrode grids can provide crucial information about the propagation of seizure activity between mesial temporal and neocortical networks, and advanced analyses of the propagation of ictal activity between these structures and others may improve localization of the ictal onset zone when planning resection.

Methods: Intracranial EEG recordings obtained during multiple seizures (3-7) were parameterized using multivariate autoregressive models (MVAR), and analyzed with short-time direct directed transfer function (SdDTF), which estimates the direction of flow between electrodes (sites), as well as the intensity, spectral content, and temporal evolution these flows. Seizures were marked at their electrographic onset, and the propagation of activity was analyzed across a wide range of frequencies (0-235 Hz).

Results: SdDTF analyses showed propagation of ictal activity between a limited number of contacts in mesial temporal regions and a larger number of neocortical sites, as well as less prominent flows among the neocortical sites themselves. These findings suggested a prominent role for mesial temporal structures in seizure generation.

Conclusions: For patients undergoing intracranial monitoring for epilepsy surgery, analyses of the patterns of EEG activity propagation between mesial temporal and neocortical networks may provide additional information that can improve seizure localization, in turn optimizing post-surgical outcomes and minimizing post-operative impairments.

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1.137

OBSERVATION OF EMERGING ICTAL NETWORK DYNAMICS USING SYNCHRONY INDEX

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Rationale: Surgical resection remains the best option for long term seizure control for patients with medically refractory focal epilepsy. Unfortunately, such treatment does not always result in seizure freedom, particularly in the long term. There is growing evidence that focal seizures may include an ictal network which may develop over time and potentially include more than one zone of seizure onset. Current presurgical evaluation applies structural and physiological imaging to identify the likely seizure onset zone. Improved techniques are required for identification of the complete ictal network both structurally and physiologically, and to establish the role of the primary seizure onset zone within the network. We demonstrate dynamic spatiotemporal changes in connectivity within the ictal network during temporal lobe seizures using a linear measure of synchrony, the Synchrony Index (SI).

Methods: We analyzed intracranial EEG data from 11 seizures from a patient with confirmed hippocampal sclerosis who is seizure free 2 years after resective surgery. A previously reported analysis demonstrated that the visually determined electrodes of seizure onset could be objectively identified using parameters derived from our Synchrony Index. EEG was recorded at 200 samples per second. Using MATLAB, the SI was calculated for every possible electrode pair combination in non-overlapping, one-second bins over the duration of the extracted file. Videos were constructed to dynamically display the highest SI value connection for each electrode for each second beginning 100 seconds preictally and ending 150 seconds after seizure onset. Still images were generated to highlight specific time points.

Results: Dynamic SI changes demonstrated clear spatiotemporal differences between the preictal, ictal and postictal time periods during 9 of 11 seizures. The preictal and postictal periods were dominated by diffuse, low SI value connections. During seizures, a nexus pattern repeatedly emerged with the electrode of visually determined seizure onset (SOZ) at the center with widespread connections. A large increase in SI value occurred first in the SOZ, then throughout the remainder of the electrodes. This was most persistent 10-20 seconds into seizures, which correlates well with our previously published data showing a large rise in SI value in the SOZ at that time. Overall, this pattern displays a network in which the majority of the recording electrodes are strongly functionally connected to the SOZ.

Conclusions: Techniques for spatiotemporal display of seizure networks are needed to augment our understanding of the pathophysiology of epilepsy and our selection of surgical candidates. We have demonstrated the use of a linear measure of synchrony to display the emergent, dynamic network patterns during a seizure in a manner that objectively highlighted the SOZ. Further investigation is required to refine this approach and improve the analysis and description of this type of data.

IMAGE: images/905776_A.jpg

Time course of typical left hippocampal seizure. (A) Representative left hippocampal onset seizure. Red arrows mark seconds 17-20. (B) Blowup demonstrating transition to higher frequency seizure activity. (LF 1 Hz, HF 70 Hz, Sens 750 ìV p-p)

IMAGE: images/905776_B.jpg

Dynamic ictal network centered on left hippocampal electrode. Pre- and post-ictal periods show diffuse patterns. Ictal period demonstrates emergence of a highly synchronous pattern focused around left hippocampal electrode 2. Dots represent intracranial electrodes. Lines display the strongest SI connection at each second. Number in parentheses is the second relative to ictal onset.

1.145

CHARACTERIZING PRE-ICTAL AND INTER-ICTAL STATES WITH GRAPH THEORETICAL APPROACHES

K. Lehnertz, Marie-Therese Horstmann and C. E. Elger (Department of Epileptology, University of Bonn, Bonn, Germany)

Rationale: Graph-theoretical approaches to a characterization of anatomical and functional brain networks has been a rapidly evolving field recently. Previous studies on epileptic brain networks reported on an increased regularization of network topology during seizures as compared to the pre- and postictal intervals, and an altered functional brain topology in epilepsy patients can even be observed during the seizure-free interval. However, these studies were based on recordings that lasted from a few seconds to several minutes only. We here investigated the time-course of graph theoretical approaches on the time scales of days particularly with respect to an identification of a pre-ictal state.

Methods: We analyzed invasive multi-day, multi-channel EEG recordings from 13 patients with focal epilepsies undergoing pre-surgical evaluation. Using a moving-window approach (duration of each window: 20.48 s corresponding to 4096 data points; no overlap) we estimated the strength of interactions (via mean phase coherence) between all pairs of sampled brain regions. We defined functional network links by thresholding the interaction matrix and estimated the global network characteristics average shortest path length L and clustering coefficient C.

Results: Both network characteristics exhibited large fluctuations over time, however with some periodic temporal structure. These fluctuations could — to a large extent — be attributed to daily rhythms while relevant aspects of the epileptic process contributed only marginally. Particularly, we could not observe clear cut changes in network states that can be regarded as predictive of an impending seizure.

Conclusions: Global statistical properties of epileptic brain networks strongly reflect daily rhythms and possibly alterations of the anticonvulsant medication. Identification of a possible pre-ictal state with graph-theoretical approaches requires a better understanding of these daily rhythms as well as further methodological developments.

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1.346

INDUCTION OF PSYCHOGENIC NON-EPILEPTIC EVENTS: SUCCESS RATES VARY WITH ICTAL SEMIOLOGY AND NEUROPSYCHOLOGICAL PROFILE

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Rationale: Psychogenic non-epileptic events (PNEE) represent paroxysmal behaviors that are caused by heterogeneous psychopathological processes rather than epileptic neuronal discharges. Three major groups of PNEE based on ictal semiology are hypermotor, hypomotor and experiential groups. Several investigators have supported the use of induction techniques for provocation of habitual PNEE of relevance, reporting success rates in the range of 77 to 84%. We hypothesize that the success rate of induction varies with ictal semiology of the presenting event of interest. Secondly, we hypothesize that neuropsychological profiles and/or demographic factors may influence the success rate of induction.

Methods: We enrolled veterans admitted to the epilepsy monitoring unit at the Michael E. DeBakey VA Medical Center from December 2008 until April 2010. Patients with epilepsy or mixed disorder of epilepsy and PNEE were excluded. According to the routine protocol at this center, provocative techniques such as photic stimulation, hyperventilation, and placebo injection are used for induction of events of interest in patients without a spontaneous event during the first 48 hours. The events of interest were categorized into three groups based on the semiologic features mentioned above. Most of the patients also completed 4 neuropsychological questionnaires: Dissociative Expressive Scale (DES), Structured Inventory of Malingered Symptomatology (SIMS), Test of Memory Malingering (TOMM), and brief COPE inventory.

Results: Demographic data of the 51 patients who were included in the analysis and their final categorization based on semiology of their event of interest is shown in the table. 24 out of 26 (92.3%) patients in the hypermotor category had successful induction of their habitual event of interest, leading to definitive diagnoses of PNEE. On the other hand, only 13 out of 20 (65%) patients in the hypomotor category had successful induction (p=0.029) (figure). Due to the small number of patients in the experiential group (n=5), the inductive success rate in this group could not be confidently assessed. Demographic and neuropsychological data were compared between the successful induction and unsuccessful induction groups. The main significant difference was the higher percentage of patients who had a SIMS score of more than 14 in the successful induction group compared to the unsuccessful induction group (p=0.035).

Conclusions: We observed that induction techniques were statistically more likely to provoke hypermotor PNEE as compared to hypomotor PNEE (p = 0.029). It can be possible that our hypomotor cases represented a wider spectrum of etiologies, including epileptic, physiologic non-epileptic, feigned, or other events not typically known to demonstrate suggestibility. Such etiologic diversity may in part explain the diminished induction success rate for hypomotor events. We observed a significant association of elevated SIMS score (> 14) among successfully induced cases, which may support the tendency toward over-reporting or exaggeration of symptoms among inducible patients.

Table - Demographic data of study subjects

IMAGE: tables/881313_T1.jpg

* Comparing hypermotor and hypomotor groups only

IMAGE: images/881313_A.jpg

3.015

EPILEPSY-INDUCED PATHOLOGIC PLASTICITY AND NMDA ALTERATIONS IN THE MALFORMED BRAIN OF HUMAN FCD PATIENTS AND MAM-PILOCARPINE RAT MODEL

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Rationale: Malformations of Cortical Development (MCDs) are developmental brain abnormalities frequently associated with drug resistant focal epilepsy. Among MCDs, type IIB Focal Cortical Dysplasia (FCD IIB) possess distinctive neuro-pathologic and clinical features, and affected patients show severe epilepsy course. To better understand the molecular and cellular mechanisms underscoring the origin and recurrence of seizures in human FCDs, we have undertaken a two-fold approach in both human and experimental settings.

Methods: We have analyzed on one side human pediatric and adult subjects with type IIB FCD surgically treated for drug-resistant focal epilepsy with a combined morphologic and molecular analysis of NMDA receptor complex composition. In addition, we have generated and characterized an experimental “double-hit” animal model by first inducing cortical malformations with prenatal exposure to methylazoxymethanol acetate (MAM) and then triggering, in adulthood, spontaneous recurrent seizures by means of pilocarpine.

Results: Our results on human subjects revealed increased expression of NMDA regulatory subunits in the post-synaptic membranes of dysmorphic neurons, which was evident in both pediatric and adult FCD patients (see Fig 1), thus indicating that abnormalities of NMDA receptor complex are consistently associated with, and may sustain epileptogenesis in FCD IIB patients. The behavioral and EEG data in our experimental model clearly demonstrated higher severity of epilepsy in MAM-pilocarpine (MAM-PILO) than naïve rats made epileptic with pilocarpine. Furthermore, the combined morphologic and molecular analysis demonstrated that chronic epilepsy worsened cortical architectural and NMDA abnormalities induced by MAM administration. Indeed, MAM-PILO rats were characterized by decreased cortical thickness and larger dysplastic pyramidal neurons with recruitment of NMDA regulatory subunits to the post-synaptic membrane, impressively resembling dysmorphic neurons of human FCD IIB (see Fig. 2). The observed abnormalities in chronic epileptic MAM-PILO rats were not due to direct pilocarpine effects or more severe epileptic status. Indeed, FluoroJade and thionine staining demonstrated more widespread cell degeneration and more evident edema in the cerebral cortex of naïve rats treated with pilocarpine alone, thus supporting that cellular/molecular abnormalities observed in the chronic epileptic MAM-PILO rats were determined by the recurrence of seizures.

Conclusions: The present data indicate that in the malformed brain a seizure-induced, cellular/molecular pathologic plasticity may play as a key actor in establishing a pathological circuitry further affecting the propensity of generating seizures.

IMAGE: images/905499_A.jpg

Fig. 1 NR2B expression in cortical pyramidal neurons of control (A and C) and FCD IIB patients (B, D-F). A-B) ICC staining shows increased NR2B signal in the FCD cortex (B) if compared to control (A). C-F) Confocal images of NR2B IF in control (C) and FCD IIB giant pyramidal neurons. Scale bars: 100 ìm in A-B, 25 ìm in A-B insets and C-F

IMAGE: images/905499_B.jpg

Fig. 2 NMDA over-expression in cortical pyramidal neurons of chronic epileptic MAM-PILO rats. A-B) A clear increase of the NR2AB signal is present in the post-synaptic membranes of cell bodies and apical dendrites (arrows in B) of pyramidal neurons of MAM-PILO as compared to MAM rats (A), with evidence of enlarged spines (arrowhead in B). C-E) Confocal IF staining of NR2AB subunits in rostral (C) and heterotopic (D) neocortex and in the hippocampus (E) of chronic epileptic MAM-PILO rats. Note that the post-synaptic NR2AB up-regulation is associated with the giant pyramidal neurons of heterotopic cortex (D). F-G) Confocal IF of NR2AB (green) - and SMI311 (red) double-labeling (F), and parvalbumin (green) and SMI311 (red) double-labeling (G) in giant dysmorphic neurons of chronic epileptic MAM-PILO rats. The arrowhead in F marks an enlarged dendritic spine. Scale bars: 25 ìm.

3.036

DIFFERENTIAL NEURONAL ACTIVATION PATTERN AND SEIZURE SUSCEPTIBILITY IN NEWBORN RAT PUPS FOLLOWING MATERNAL STRESS AND IMMUNE CHALLENGE

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Rationale: The underlying pathophysiology in the majority of pediatric epilepsies is still incompletely understood. To improve this understanding new models are needed that mimic the reality that most cases of pediatric epilepsy are non-lesional and unlikely to be from a single gene abnormality. Herein we describe the behavioral and anatomical features of a new model of seizure susceptibility.

Methods: Groups of three pregnant Sprague Dawley female rats were transported either during early (EG), or middle (MG), gestation and subsequently assigned to one of three groups: naïve, control (saline i.p.) or experimental (LPS; 100 µg/kg i.p.). Injections were performed on the 15th day of gestation (G15). Pregnancy and parturition then proceeded undisturbed and pups remained with their mothers. Pups were then challenged with a febrile convulsions (FC) paradigm on the 14th post natal day (P14) involving an injection of 200 µg/kg of LPS followed 2.5 hours later by 1.75 mg/kg of kainic acid and videotaped for 3 hours for behavioral scoring. Twenty-four hours after seizure provocation animals were euthanized and their brains processed for immunohistochemical reactivity (IR) and analysis of FosB, c-fos, c-jun, protein expression as well as Fluoro-jade C expression using standard procedures.

Results: The paradigm did not adversely affect parturition nor alter the typical litter size or sex ratio. Maternal transport during later gestation however resulted in increased pup seizure severity and more lethal events ($p<0.001$). Both prenatal saline and LPS at G15 decreased pup seizure severity in a graduated manner: an effect that was seen at both transport times ($p<0.05$ to $p<0.001$). Qualitative and quantitative immunohistochemical analysis revealed significant differences in FosB-IR expression in the hippocampal subregions, amygdala, piriform, entorhinal and retrosplenial cortices, nucleus accumbens, periventricular regions of both the thalamus and hypothalamus, the substantia nigra and the locus coeruleus ($p<0.05$ to $p<0.001$). Similar patterns were observed in the IR expression of c-fos and c-jun with slight variations. This differential expression did not appear to be a result of cell death as there was minimal expression of Fluoro-jade C.

Conclusions: These results suggest that maternal prenatal stress and immune challenge modify newborn seizure susceptibility and that the magnitude and direction of the effect was dependent on the timing of the stressor(s). Further, the combination of the FC-induced behavioral

manifestations and neuronal activation pattern in the P14 pups suggests a change in the circuit activation that was related to the maternal prenatal stress. Ongoing studies are examining both the underlying pathophysiological mechanisms of the model, as well as the impact of the prenatal stressors on neurodevelopment and epileptogenesis.

3.045

LOW BLOOD GLUCOSE INCREASES ABSENCE SEIZURE SUSCEPTIBILITY

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Rationale: Absence epilepsies are a common disease with a strong genetic aetiology. Certain environmental factors can influence absence occurrence but a complete understanding of absence precipitation is lacking. Here we investigate if lowering blood glucose increases spike-wave activity in mouse models with varying seizure susceptibility.

Methods: Three mouse models were used; an absence seizure model based on the knock-in of a human GABAAã2(R43Q) mutation (DBA(R43Q)), the spike-wave discharge (SWD)-prone DBA/2J strain, and the seizure resistant C57Bl/6 strain. Electrocorticogram recordings were made to measure SWDs from mice prior to and following injection of various doses of insulin. Blood glucose was independently measured to determine the reduction in levels following insulin injection.

Results: A ~45% reduction in blood glucose levels (6.7±0.3 mM to 4.0±0.4 mM, n=10, $p<0.05$) was sufficient to double SWD occurrence in the DBA(R43Q) model (19.9±5.9 to 50.3±5.9 SWD/h, n=10, $p=0.001$) and in the SWD-prone DBA/2J mouse strain(1.1±0.5 to 1.8±0.4 SWD/h, n=7, $p=0.01$). Larger reductions in blood glucose further increased SWDs in both these models. However, even with large reductions in blood glucose no discharges were observed in the seizure-resistant C57Bl/6 mouse strain (n=6). Injection of glucose reversed the impact of insulin on SWDs in the DBA(R43Q) model (48.5±14.2 to 20.5±9.8 SWD/h, n=5, $p=0.02$), supporting a reduction in blood glucose as the modulating influence.

Conclusions: Low blood glucose can reduce seizure threshold in genetically predisposed animal models and should be considered as a potential environmental risk factor in absence epilepsy patients.

3.053

FAST RIPPLES IN AN EXPERIMENTAL NON-LESIONAL TEMPORAL LOBE EPILEPSY

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Rationale: Very fast ECoG activity, especially >250 Hz ("fast ripples"), has been implicated in epileptogenesis and seizure generation. Previous reports have concentrated on temporal lobe epilepsy with hippocampal sclerosis in both chronic experimental models and clinical cases. Here we determine whether fast ripples also provide a marker for the epileptic focus in an experimental temporal lobe epilepsy with no detectable neuronal loss.

Methods: We induced epileptic foci in anaesthetised rats by unilateral intrahippocampal injection of tetanus toxin, and implanted electrodes into ipsi- and contralateral CA3 and either CA1 or dentate gyrus. Recordings started 3-6 days after the operation, with sessions of a few hours repeated up to 21 days. At the end of the recordings the rats were killed by anaesthetic overdose and their brains were prepared for histology.

Results: A total of 60 electrographic seizures were recorded from 10 rats. The interictal periods were characterised by interictal discharges, typically lasting under 100 ms, and repeated epileptic discharges or polyspikes lasting a few seconds. 73% of seizures were first detected by the electrodes in the injected hippocampus, while interictal discharges could occur in either hippocampus alone or in both within a few ms. High-frequency activity was superimposed on both interictal and ictal activity and was analysed in both the frequency and time domains. The first spectral moment and the ratio between the powers of ripples (100-250 Hz) and fast ripples (251-600 Hz) both were higher in the injected hippocampus. These differences could be attributed to the more frequent occurrence of fast ripples in the injected hippocampus, and the similar rates of occurrence of ripples in the two hippocampi. Similar differences in high-frequency activity were recorded between the two sides during seizures.

None of the 7 rats that were analysed histologically showed evidence of neuronal loss.

Conclusions: Fast ripples can occur in epileptic foci lacking any discernible neuronal loss, and certainly without hippocampal sclerosis. In the tetanus toxin model fast ripples were always more common in the injected hippocampus, unlike interictal discharges and ripples, both of which were equally likely to occur in either hippocampus. We conclude that fast ripples are a more reliable marker for the primary epileptogenic zone than other kinds of interictal activity. Fast ripples should be considered for their potential contribution to pre-surgical work-up of non-lesional temporal lobe epilepsy.

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3.062

A CLOSED-LOOP IMPLANTABLE DEVICE FOR EPILEPTIC SEIZURE DETECTION AND NEUROSTIMULATION

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Rationale: Some patients with pharmacoresistant partial epilepsy are not candidate for surgery. There has been growing interest in neuro-responsive intracerebral local treatment of seizures such as focal drug delivery, focal cooling, or electrical stimulation. The latter requires an effective seizure-detection system and a brain stimulator. We present a low-power implantable integrated device for responsive electrical stimulation.

Methods: The proposed implantable closed-loop neuro-stimulator (CLNS) combines an epileptic seizure detection (EPSD) with simultaneous electrical stimulation feedback. The EPSD provides

continuous long-term monitoring of intracerebral EEG (iEEG). The sensitivity of EPSD is enhanced and several decision boundaries are introduced to reduce the number of false alarms for the patient-specific seizure pattern. The seizure-onset information is extracted through early modulation and proper rectification of the intracerebral signal. The EPSD determines the high-frequency patterns and the progressive amplitude increase of the seizure signal. The iEEG is analyzed over a certain time frame and a higher number of the detection indicates an upcoming seizure event.

Results: The EPSD algorithm was validated through behavioral simulations in MATLAB. The EPSD was implemented and fabricated in a 0.18-µm CMOS technology. The EPSD circuits fit in 2 mm X 1 mm chip area. Mixed-mode (analog/digital) tuning circuitry was used to enable adjusting the amplitude threshold and the time frame of the seizure-onset detection. Thus, this EPSD chip can be adapted to the patient' specific seizure onset pattern. Furthermore, it can be tuned to be non-responsive to high-frequency brief electrical seizures if needed. This EPSD chip demonstrated accurate detection of seizure onsets, based on iEEG recordings from 8 patients with epilepsy. Furthermore, the influence of low-frequency noise was found to be negligible. Moreover, the total power dissipation was less than 6.80 µW. The electrical stimulator has been highly miniaturized. The external controller provides energy and transmits data to the implanted stimulator by means of inductive coupling of spiral antennas. The control unit of the implanted stimulator is based on a commercially available Field Programmable Gate Array (FPGA) that present advantageous low-power and small-scale features. The CLNS is assembled on two circular printed circuit boards (PCB) of 2 cm diameter each, which are connected together with a flexible bus connector. The power consumption of the CLNS has showed that the system could run on a button cell battery for more than 8 years.

Conclusions: The experimental results demonstrated the detection accuracy and the low-power dissipation of this implantable CLNS.

3.212

CLUSTER ANALYSIS APPLIED TO FMRI DATA IN TYPICAL CHILDHOOD ABSENCE SEIZURES

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Rationale: Typical childhood absence seizures (CAS) are brief 5-10 second episodes, accompanied by short-term impairment of consciousness, and by 3Hz spike-and-wave discharges which begin and end abruptly on EEG. Recently, functional magnetic resonance imaging (fMRI) with simultaneous EEG recording has been instrumental for our current understanding of the anatomical and functional basis of CAS. These EEG-fMRI studies typically have used a general linear model (GLM) with a pre-defined hemodynamic response function (HRF) to assess dynamic changes of blood-oxygenation-level-dependent (BOLD) signal in whole brain, which reflects neuronal activation, albeit indirectly. However, there is some important evidence that the actual hemodynamic response for diverse brain regions may differ from the standard HRF.

Methods: We performed a model-free clustering approach to investigate BOLD changes during 51 CAS in 8 pediatric patients with typical childhood absence epilepsy (CAE). This approach has three steps, 1) the time courses of single voxels during the time period from -20s to +40 s relative to seizure onset were averaged across patients. 2) 116 gray matter anatomic volumes of interest (AVOI) were pre-defined from the SPM2 MRI template (MARSBAR), and the temporal correlations between pairs of mean time courses of AVOIs were computed. The number of expected clusters was determined by analyzing these correlations using a hierarchical clustering method. 3) Correlations between each pair of time courses of voxels were computed. Then we performed a k-mean method to create partitions of voxels exhibiting similar time courses, using the number of expected clusters obtained from step 2.

Results: We found that 116 AVOIs can be divided into four clusters by using the hierarchical clustering method. By applying the k-mean method, the partition of areas into clusters emerged as follows: 1) thalamus and occipital cortex; 2) lateral and part of medial parietal cortex, medial temporal, basal ganglia, and cerebellum; 3) part of medial frontal, lateral frontal, orbital frontal, and rolandic cortices; 4) part of medial frontal, medial parietal, medial temporal cortices and insula. Furthermore, we observed that fMRI change of the cluster involving thalamus and occipital cortex was closer to the conventional HRF, and changes of the other three clusters appeared to differ greatly from the conventional HRF.

Conclusions: Our results demonstrate a complex sequence of fMRI changes in absence seizures, which are not detectible using conventional HRF modeling. These results also revealed that current clustering methods can effectively identify regions of similar activation. Finally, our present findings suggest that the clustering method might be a very useful tool for analysis of activation patterns in fMRI for other types of generalized seizures.

3.339

DYNAMIC DISINHIBITION OF CORTICAL CIRCUITS

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Rationale: Epileptic syndromes are frequently accompanied by changes in interneuron properties and numbers. Parvalbumin-positive (FS) interneurons exert strong perisomatic inhibition onto cortical pyramidal cells and can veto spike generation. To investigate their influence on cortical circuit properties we dynamically silenced FS interneurons via activation of the light-gated chloride pump halorhodopsin (eNpHR). We hypothesize that silencing of FS interneurons leads to a pronounced enhancement of cortical excitability.

Methods: Mice (3-4 weeks old) expressing cre-recombinase under the control of the parvalbumin promoter (parv/cre-mice) were infected with an AAV vector ("AAV5-EF1a-DIO-eNpHR3.0-EYFP") containing a doublefloxed eNpHR-EYFP construct controlled by the EF-1a promoter. Virus was stereotaxically injected into each hemisphere of the primary somatosensory cortex. Expression efficiency and localization were evaluated using EYFP fluorescence at time points from 10 days to 7.5 weeks post injection. Activation of eNpHR was achieved using a xenon arc lamp that illuminated the slice through the microscope objectives and a 593 +/- 20 nm (yellow) bandpass filter. Inhibitory and excitatory postsynaptic responses were evoked by electrical stimulation and laser-scanning photostimulation/glutamate uncaging (LSPS), and cells were recorded in current and voltage clamp using standard techniques.

Results: Strong EYFP expression was detected up to 1 mm from the injection site. Healthy fluorescent cells were observed 2-4 weeks post injection, but by 5 weeks post injection, many strongly fluorescent cells had formed inclusion bodies and were no longer suitable for electrophysiological recordings. Subsequent experiments were therefore conducted 2-3 weeks post injection. Fluorescent cells had light-activated currents of -195 +/- 65 pA (n=14), corresponding to a hyperpolarization of 24 +/- 10 mV. Stimulation in layer 2/3 elicited complex postsynaptic responses in layer 5 pyramidal cells, consisting of an early EPSC and a later IPSC, which presumably originated via mono- and disynaptic activation, respectively. In the presence of yellow light the IPSC component was reduced or absent in over 50% of recorded cells. In current clamp recordings, repetitive activation of eNpHR by trains of yellow light caused a 2-3-fold increase in spike output at all stimulation frequencies tested (10, 50 and 100 Hz).

Conclusions: These experiments demonstrate the feasibility of a) directing eNpHR expression to FS cells in somatosensory cortex and b) eNpHR mediated disinhibition of pyramidal cells. These methods can now be used to investigate the specific role of FS interneurons in controlling epileptiform activity in slices, and seizures in vivo.

3.340

ABERRANT INTEGRATION OF POSTNATALLY GENERATED NEURONS IS SUFFICIENT TO CAUSE EPILEPSY

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Rationale: Adult generated hippocampal dentate granule cells have been implicated in the development of epilepsy. Following an epileptogenic brain insult, these cells integrate abnormally, leading to characteristic pathologies of the epileptic brain, including the appearance of ectopic cells, cells with aberrant basal dendrites and mossy fiber sprouting. Recurrent excitatory circuits created by these pathologies are hypothesized to promote hyperexcitability and seizures. Direct evidence in support of this hypothesis, however, is limited.

Methods: Here, we sought to determine whether abnormal granule cells are sufficient to cause epilepsy. Using conditional, inducible triple-transgenic Gli1-CreERT2 X PTENflox/flox X GFP reporter mice we were able to selectively disrupt the development of postnatally generated neurons. Triple transgenic animals were treated with tamoxifen on P14, leading to the deletion of PTEN (phosphatase and tensin homologue) and activation of GFP expression in a subset of subgranular and subventricular zone progenitors.

Results: PTEN deletion was highly selective, with a subset of granule cells and olfactory neurons being the only neuronal populations affected in the CNS. PTEN deletion from granule cells reproduced key abnormalities of the epileptic brain, including formation of basal dendrites, ectopic migration to the hilus, and mossy fiber sprouting. Acute hippocampal slices prepared from PTEN deleted animals revealed hyperexcitability in this region. Moreover, animals exhibited longer evoked seizures when challenged with flurothyl. Finally, 24/7 video-EEG monitoring confirmed that these animals were spontaneously epileptic, exhibiting frequent seizures by three months of age.

Conclusions: Abnormal granule cells are a hallmark of temporal lobe epilepsy, and are present in both epileptic animals and humans. For decades, it has been unclear whether these abnormal cells are a cause or consequence of epilepsy. The present study provides new evidence indicating that disruption of postnatally generated neurons is capable of causing epilepsy, and morphological and physiological data strongly implicates hippocampal granule cells, rather than olfactory neurons, in this process. Future studies will focus on determining whether these cells are necessary for epileptogenesis.

3.357

TEMPORAL LOBE EPILEPSY INDUCED INCREASES IN PERSISTENT (INAP) AND RESURGENT (INAR) NA CURRENTS

Manoj K. Patel, N. J. Hargus and E. H. Bertram (University of Virginia, Charlottesville, VA)

Rationale: Temporal lobe epilepsy (TLE) is a common form of adult epilepsy involving the limbic structures of the temporal lobe. Layer II neurons of the entorhinal cortex (EC) form the major excitatory input into the hippocampus via the perforant path and consist of non-stellate and stellate neurons. These neurons are spared and hyper-excitable in TLE. Since sodium (Na) channels play a critical role in action potential (AP) generation and conduction we sought to determine if Na channel gating parameters and expression levels were altered in TLE. Specifically we focused on persistent (INaP) and resurgent (INaR) Na currents since these two currents arise mainly from activation of the Nav1.6 Na channel isoform and are major contributors to the generation of AP bursts.

Methods: Brain slices were prepared from control rats and rats with TLE. INaP and INaR currents were recorded from visually identified EC layer II non-stellate and stellate neurons.

Results: Both TLE stellate and non-stellate neurons had larger INaP current amplitudes when compared to control neurons. In non-stellate neurons control INaP currents had an amplitude of -121.3 ± 26.1 pA (n = 9) and were significantly ($P<0.01$) increased in TLE to -358 ± 46.2 pA (n = 7). In a similar manner, TLE stellate neurons also had increased INaP current amplitudes. Amplitudes were increased from -153.5 ±18.9 pA (n = 9) under control conditions to -356.8 ± 31.7 pA (n = 7: $P < 0.01$) in TLE.

INaR current amplitudes were also increased in TLE. INaR currents in non-stellate neurons were profoundly increased from -514.8 ± 72.4 pA (n = 6) in control to -1394.6 ± 82.1 pA (n = 7: $P < 0.001$) in TLE. INaR currents in stellate neurons were also significantly larger in TLE compared to controls. Control amplitudes were increased from -568.9 ± 58.9 pA (n = 7) to -1477.8 ± 75.2 pA (n = 7: $P < 0.001$) in TLE. Families of INaR currents were evoked to construct current voltage plots. TLE non-stellate neurons had significantly ($P<0.05$) hyperpolarized INaR V1/2 values (-61.3 ± 1.9; n=7 in control compared with -68.0 ± 2.3; n=8 in TLE). Slopes were also slowed in TLE (-5.0 ± 0.6 in control compared with -6.2 ± 0.5 in TLE). In contrast to non-stellate neurons, INaR V1/2 values in stellate neurons were unchanged (-70.1 ± 2.8; n=10: in control compared with -65.4 ± 2.9; n=6 in TLE). Slope values were slowed in TLE (-4.0 ± 0.4 in control compared with -7.0 ± 0.4 in TLE; $P<0.05$). Immunohistochemistry experiments revealed increased staining intensity of Nav1.6 along the axon initial segment (AIS) in TLE brain slices when compared to control.

Conclusions: We propose that increases in INaR and INaP in TLE may contribute to the generation of AP bursts previously reported in

EC layer II neurons in TLE, leading to seizure generation and spread within the limbic system.

Monday, December 6, 2010

Poster Session 3
8:00 a.m.-3:30 p.m.

3.001

ADENOSINE KINASE IS A TARGET FOR THERAPEUTIC ANTISENSE STRATEGIES IN EPILEPSY

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Rationale: Given the high incidence of refractory epilepsy, novel therapeutic approaches and concepts are urgently needed. To date, viral mediated delivery and endogenous expression of antisense sequences as a strategy to prevent seizures has received little attention in epilepsy therapy development efforts. Here we validate adenosine kinase (ADK), the astrocyte-based key negative regulator of the brain's endogenous anticonvulsant adenosine, as therapeutic target for antisense-mediated seizure suppression.

Methods: We developed adeno-associated virus 8 (AAV8)-based gene therapy vectors to selectively modulate ADK expression in astrocytes. Cell type selectivity was achieved by expressing an Adk-cDNA in sense (to overexpress ADK) or antisense (to knockdown ADK) orientation under the control of an astrocyte-specific gfaABC1D promoter. Viral vectors (10^12 genomic particles per ml) where injected into the CA3 hippocampal subfiled of wild-type mice (n=4) or spontaneously epileptic Adk-tg transgenic mice (n=4) that show a global, brain-wide overexpression of ADK (141% of normal). An AAV8-Gfa-null virus was used as control (n=4). After virus injection ADK expression was assessed histologically and biochemically. In addition, animals were subjected to 12-hour sessions of continuous intracranial EEG-monitoring using intrahippocampal bipolar electrodes placed into the CA3 region.

Results: We demonstrate in wild-type mice that viral overexpression of ADK (145% of normal) within astrocytes of the CA3 region is sufficient to trigger spontaneous recurrent seizures in the absence of any other epileptogenic event. Seizures in the Adk-sense injected mice were frequent in terms of the average number of seizures per hour (6.6 + 0.21, ***p = 0.0001) and the long seizure duration (81.2 + 0.6 sec, ***p = 0.0002) compared to related events recorded in null virus injected control animals (1.38 + 0.38 seizures per hour, duration = 45.3 + 7.8 sec). These results were confirmed by western blot analysis of ipsi- and contralateral hippocampal protein extracts from Adk-SS injected mice (n = 2). Additionally, AAV8-mediated RNA interference almost completely abolished spontaneous recurrent seizures in Adk-tg mice (**p=0.006) compared to null virus injected Adk-tg mice.

Conclusions: Our data demonstrate that over- or underexpression of astrocytic ADK in the absence any epileptogenic factor is sufficient to trigger or prevent seizures, respectively. This is the first study to use an antisense approach to validate ADK as a rational therapeutic target for the treatment of epilepsy and suggests that gene therapies based on the knock down of ADK might be a feasible approach to control seizures in refractory epilepsy.

3.002

SINGLE-CELL KNOCKOUT OF TSC1 IN UTERO GENERATES CORTICAL TUBER-LIKE LESIONS AND HETEROTOPIC NODULES WITH CYTOMEGALIC NEURONS

David Feliciano, T. Su and A. Bordey (Yale University School of Medicine, New Haven, CT)

Rationale: Tuberous Sclerosis Complex (TSC) is a multisystem genetic disorder characterized by mutations in Tsc1 or Tsc2 leading to mammalian target of rapamycin (mTOR) hyperactivity. 80-90% of TSC individuals suffer from intractable seizures resulting from cortical malformations (called tubers) which form during embryonic life. Understanding how these lesions form and lead to hyper-excitability has been limited by the absence of an animal model exhibiting tubers.

Methods: To address this limitation, we used in utero electroporation of Cre recombinase-containing vector in transgenic mice carrying a floxed and a mutant Tsc1 allele for knocking out Tsc1 in selected neuronal populations at a precise developmental time-point.

Results: Single-cell knockout of Tsc1 led to increased mTOR activity and soma size of Tsc1 null neurons. This approach generated heterotopic nodules above or in the white matter and discrete cortical tuber-like lesions displaying a mosaic of cell size and phospho-S6 immunoreactivity. The electroporation time-point determined the severity of the malformations with late-born cortical structures being the most affected. Tuber-like lesions display ectopic neurons resulting in loss of cortical architecture, cytomegalic and multinucleated neurons with abnormal dendritic trees resembling giant cells. No gliosis was visible and phospho-pS6 immunoreactivity was surprisingly not up-regulated in Tsc1 null astrocytes despite a lower seizure threshold.

Conclusions: These data suggest that a double-hit strategy to eliminate Tsc1 in discrete neuronal populations generates TSC-associated cortical lesions providing a model to uncover the mechanisms of lesion formation and hyper-excitability.

3.003

ADK ANTISENSE VIRUS REDUCES SEIZURE SUSCEPTIBILITY FOLLOWING SEVERE TRAUMATIC BRAIN INJURY

Theresa A. Lusardi, N. Lytle and D. Boison (Robert S. Dow Neurobiology Labs, Portland, OR)

Rationale: Post traumatic epilepsy (PTE) is the cause of 20% of symptomatic epilepsy. While the precipitating brain injury is well-identified, the incidence, progression, and treatment of PTE are not well understood. Astrogliosis is a common consequence of severe brain injury. We have demonstrated that astrogliosis, associated with overexpression of adenosine kinase and resulting adenosine deficiency, is linked to hippocampal hyperexcitability. We hypothesized that by blocking the ADK upregulation, we could maintain an adenosinergic tone in the injured brain, and thus minimize seizure susceptibility following severe TBI.

Methods: Male Sprague Dawley rats (n=15) received severe TBI by fluid percussion injury (FPI). 48 hours after FPI, they received either

vehicle injection (lactated ringers, n=9) or an AAV8 virus expressing ADK mRNA antisense with a GFP promoter (1x1010 genomic particles/ml). Vehicle or virus injection was disbursed in the hippocampus (3 µl) and the cortex (3 µl) at the site of FPI. The GABA inhibitor pentylenetetrazol (PTZ, Sigma) was used to assess seizure susceptibility. Pretreatment with the adenosine A1 receptor antagonist DPCPX (8-Cyclopentyl-1,3-dipropylxanthine, Sigma) was used to assess the role of adenosine in seizure susceptibility.

Results: The PTZ seizure threshold in severely injured rats with vehicle treatment was 35.0 +/- 3.5 mg/kg, not significantly different from naïve rats (35.5 +/- 3.2 mg/kg). However, in the severely injured rats with ADK-antisense virus, the threshold increased to 44.2 +/- 5.1 mg/kg PTZ. In a subsequent study, seizure severity was assessed by the Racine scale following three PTZ administrations (25mg/kg): baseline PTZ, DPCPX + PTZ, and PTZ alone. A minimum of 48 hours passed between tests. For the baseline PTZ test, there was no difference among the groups, with an average Racine score of 2.9 for naïve, 3.2 for severe FPI+vehicle, and 3.0 for severe+ADK-antisense treated rats. When the PTZ treatment was preceded by DPCPX, the naïve rats' average Racine score was 3.1, and the Severe+ADK antisense 3.0. However, the Severe+vehicle treated animals Racine score increased to 4.0. A final PTZ dose showed a PTZ response similar to the baseline Racine score, indicating the absence of kindling in these studies.

Conclusions: Our data demonstrate (i) that epileptiform bursts already occur within a short time span (4-6 weeks) after severe TBI, (ii) that those epileptiform bursts determine seizure susceptibility, and (iii) that an ADK antisense approach can be used to reduce seizure susceptibility following TBI. These results are of importance regarding therapeutic prospects for both civilian and military victims of TBI.

3.004

LOSS OF GABAERGIC TONIC INHIBITION IN A MOUSE MODEL OF ABSENCE EPILEPSY CORRELATES WITH DECREASED THALAMOCORTICAL BURSTING IN VITRO

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Rationale: Cope and colleagues recently showed that several animal models of absence epilepsy involve increases in GABAergic tonic inhibition (Nat Med 2009; 15:1392). In contrast, a loss of tonic inhibition could also lead to hyperexcitability and seizures. The ã2R43Q mutation of the GABAA receptor causes hereditary Generalized Epilepsy with Febrile Seizures Plus (GEFS+) in humans (Nat Genet 2001; 28:49) and absence-like seizures in knock-in mice (PNAS 2007; 104:17536). In heterologous expression systems, mutant receptors have altered kinetics (Mol Pharmacol 2009;77:35) and expression (J Biol Chem 2004; 279:47034; J Neurosci 2006; 26:2590), differentially affecting phasic and tonic inhibition (J Neurosci 2007; 27:14108). We previously demonstrated this mutation abolishes inhibitory tonic currents in thalamic relay and cortical pyramidal neurons, and decreases currents activated by ä-subunit selective ligands in thalamic relay cells. The loss of this conductance is expected to cause depolarization that could affect the ability of thalamic neurons to fire calcium-dependent bursts. Here we used a multichannel recording technique to examine spontaneous bursting activity throughout the thalamocortical loop in slices from 16-24 day old wild-type (WT) and heterozygous ã2R43Q knock-in mice.

Methods: Multichannel recordings were made with two NeuroNexus 16-channel recording arrays placed in thalamus and cortex of 400 µm thalamocortical slices. Neurons were isolated using a principal components-based clustering and spike sorting algorithm. Long recordings (> 60 min) consisted mainly of sparse spiking, punctuated by brief periods of high intensity activity, leading to bimodal interspike interval (ISI) distributions with peaks at <10 and >100 ms. We therefore defined a burst as two or more spikes with ISIs of less than 50 ms. For each cell, the tendency to fire in bursts was defined by the burst ratio: (# of bursts events divided by # of lone spikes). Bursting correlational coefficients were computed for all cell combinations for comparison.

Results: For WT (n = 5 slices) and ã2R43Q (n = 4 slices) mice, there were no differences in overall firing rates (Hz) for any condition (Kruskal-Wallis test: median, IQR; thal p e" 0.17: WT: 0.05, 0.1: 102 cells; ã2R43Q: 0.03, 0.09: 68 cells; ctx: WT: 0.04, 0.2: 86 cells; ã2R43Q: 0.03, 0.08: 57 cells). Compared to WT, burst ratios were decreased by ~50% for ã2R43Q in both the thalamus and cortex (thal $p<0.0001$: WT: 0.7, 1.2; ã2R43Q: 0.3, 0.6; ctx $p<0.001$: WT: 0.2, 0.5; ã2R43Q: 0.1, 0.3). WT mice express strong intra-area and thalamocortical bursting correlations, while RQ mice show decreased correlations in intra-area bursting and thalamocortical burst correlations were completely lost.

Conclusions: These results are consistent with the loss of tonic inhibition promoting depolarization of thalamic neurons, causing a switch from burst- to tonic-firing modes, and an apparent breakdown of thalamocortical communication. It remains unclear how such a breakdown might set the stage for hypersynchronous thalamocortical absence seizures.

IMAGE: images/908307_A.jpg

3.005

WHICH TYPE OF ADENOSINE RECEPTORS MAY SUPPRESS CORTICAL EPILEPTIC AFTERDISCHARGES?

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Rationale: Recently we demonstrated that nonspecific adenosine receptor agonist 2-chloroadenosine exhibits marked anticonvulsant action against cortical epileptic afterdischarges (ADs) in immature rats. We decided to differentiate a role of two types of adenosine receptors present in the brain (A1 and A2A) in this action.

Methods: Rats 12, 18 and 25 days old with implanted epidural stimulation and recording electrodes were studied. Fifteen-second stimulation series consisted from 1-ms biphasic pulses delivered at 8-Hz frequency. These stimulation series were repeated six times with 10-min intervals, intensity was just suprathreshold for elicitation of ADs. Drugs were injected 5 min after the first AD. Agonists of A1 (CCPA) and A2A receptors (CGS21680) as well as antagonists (DCPCX for A1 and ZM241385 for A2A receptors) were administered in two different doses according to our data from experiments with pentetrazol-induced seizures. Control animals received either saline (control for CCPA) or dimethylsulfoxide (controls for the three other drugs). Duration of the ADs was measured and motor phenomena (movements during stimulation and clonic seizures accompanying ADs) were quantified.

Results: Repeated stimulation resulted in progressive prolongation of ADs in control rats, especially in 12-day-old ones. Duration of ADs

was extremely (up to 17fold) prolonged by A1 receptor antagonist DPCPX, and shortened by an agonist CCPA. This effect was more marked in 12-day-old rats and moderate (effect of the antagonist) or nearly negligible (effect of the agonist) in 25-day-old ones. Drugs affecting A2A adenosine receptors did not significantly influence duration of ADs, only a tendency to suppression of progressive prolongation was observed with both agonist CGS21680 and antagonist ZM241385 in 12-day-old animals. None drug influenced movements induced directly by stimulation as well as clonic seizures forming a motor counterpart of ADs.

Conclusions: Adenosine action on A1 receptors is the mechanism of its anticonvulsant action in a model of cortical seizures. The role of these receptors is more important at early than at later developmental stages what indicates that agonists of A1 adenosine receptors may be a source of anticonvulsants specific for infant and early childhood epilepsies.

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3.006

LONG-LASTING ALTERATIONS IN NKCC1 AND KCC2 EXPRESSION INDUCED BY EVOKED AND SPONTANEOUS SEIZURES IN KINDLED EPILEPTIC RATS

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Rationale: GABAA inhibition powerfully controls emergent properties such as recurrent excitation and network synchronization, and is mediated by a Cl" conductance whose direction and functional effects depend on the Cl" gradient maintained by the electroneutral ion co-transporters NKCC1 and KCC2, which are driven by cation gradients generated by Na+-K+ ATPases and alter [Cl-]i without net movement of charge across the membrane. NKCC1 inwardly transports Cl- and contributes to [Cl"]i in immature neurons, while KCC2 extrudes Cl- and contributes to the transition from depolarizing to hyperpolarizing GABA responses in maturing postnatal neurons. Given the importance of the Cl" gradient for GABAA inhibition and network excitability, it was of interest to determine if repeated seizures that define epilepsy and the progression of seizures and permanent network alterations induced by brief repeated seizures evoked by kindling alter expression of NKCC1 and KCC2. Western blotting and immunohistochemistry were used to quantify expression of NKCC1 and KCC2 in the hippocampus of kindled adult rats that experienced partial seizures (Class I-IV), 3-75 evoked secondary generalized (Class V) seizures, or spontaneous Class V seizures.

Methods: Conventional western blot and immunohistochemical methods with antibodies to NKCC1 (T4 mouse monoclonal antihuman colonic T84 epithelial Na+-K+-Cl- co-transporter) or KCC2 (rabbit polyclonal anti-K+-Cl- cotransporter) were used to assess expression in hippocampal extracts and brain sections at ~24hrs or > 3 months after the last evoked seizure.

Results: NKCC1 expression increased in rats after induction of Class V seizures compared to control animals without seizures (p d" 0.05)or rats experiencing only partial seizures (Class I-IV), and increased to a maximum at ~75 Class V seizures. There were no further increases after >100 Class V seizures, a kindling stage associated with spontaneous seizures. Seizure-induced increases in NKCC1 expression were long-lasting and were noted as long as 3 months after 23-27 evoked Class V seizures. In contrast, KCC2 expression was not increased compared to controls except for a modest increase after 100 Class V seizures (pd" 0.05). Immunohistochemical analysis revealed regional alterations of expression in the hippocampal subfields and the dentate gyrus.

Conclusions: Repeated evoked secondary generalized seizures but not partial seizures induced robust long-lasting increases in expression of NKCC1 followed by modest increases in KCC2 expression at kindling stages associated with spontaneous seizures. The functional effects of the long-lasting chronic increase in NKCC1 prior to emergence of spontaneous seizures include Cl" loading that could influence E(Cl-), E(ipsp), or E(GABAa)as well as activity-dependent alterations in trans-membrane ionic gradients contributing to network synchronization and progressive adverse consequences of repeated seizures.

3.007

BLOCKING EARLY GABA DEPOLARIZATION WITH BUMETANIDE RESULTS IN PERMANENT ALTERATIONS IN CORTICAL CIRCUITS AND SENSORIMOTOR GATING DEFICITS

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Rationale: The highest incidence of seizures occurs during the neonatal period when immature networks are hyperexcitable and susceptible to synchronized activity. During development, GABA, the primary inhibitory neurotransmitter in adults, excites neurons due to high expression of the Na^+-K^+-$2Cl^-$ cotransporter (NKCC1). NKCC1 facilitates seizures because it renders GABA activity excitatory through intracellular Cl^- accumulation, while blocking NKCC1 with bumetanide suppresses seizures. Bumetanide is currently being tested in clinical trials for treatment of neonatal seizures.

Methods: Pregnant mice and their postnatal pups were treated with daily intraperitoneal injections of bumetanide at 0.2 mg/kg. We performed whole-cell patch clamp recordings in cortical pyramidal neurons to record miniature postsynaptic current to assess for synaptic connectivity. We studied neuronal morphology by using in utero electroporation of GFP-expressing plasmids and 3D reconstruction of their morphology using confocal microscopy. We also performed a battery of behavioral tests to assess for any developmental and permanent functional deficits in treated mice.

Results: By blocking NKCC1 with bumetanide during cortical development, we found a critical period for the development of AMPA synapses. Disruption of GABA signaling during this window resulted in permanent decreases in excitatory synaptic transmission and sensorimotor gating deficits, a common feature in schizophrenia.

Conclusions: Our study identifies an essential role for GABA-mediated depolarization in regulating the balance between cortical excitation and inhibition during a critical period and suggests a cautionary approach for using bumetanide in treating neonatal seizures.

IMAGE: images/902257_A.jpg

Blocking NKCC1 with bumetanide during a critical period disrupts the balance of excitatory and inhibitory synapses in the adult. (A) and (B) Current traces of mPSCs of layer II cortical neurons recorded from 4 week old and adult mice treated with either saline (PBS) or bumetanide from E15-P7. Traces on the right represent expanded segments of traces

on the left. (C) Frequency of AMPA (left) and GABA (middle) mPSCs for different windows of bumetanide exposure. Ratio of GABA to AMPA mSPCs (right) shows that bumetanide treatment from E15-P7 and E17-P7 resulted in significant increases due to defects in forming excitatory AMPA synapses (D) Same parameters analyzed in (C) but in 8-12 week old adult mice. Bar graphs indicate mean ± SEM, number of recorded cells is indicated in each bar graph. (*p<0.01, **p<0.001, ***p<0.0001 compared to control; t-test).

IMAGE: images/902257_B.jpg

Bumetanide treatment causes deficits in sensorimotor gating (A) Prepulse inhibition of the startle response testing for sensorimotor gating functions. Different startle amplitudes (in newtons) in response to the 120dB stimulus (stim) are graphed against the different prepulse (pp) values. (B) Prepulse inhibition is measured by the degree to which the maximal startle response is inhibited by the prepulse stimulus. Bar graphs indicate mean ± SEM (n = 29 animals per condition). (C) Post hoc analysis of mice with similar startle response amplitudes demonstrates that even in mice matched for maximal startle, bumetanide-treated animals exhibit significant decrease in their prepulse inhibitions (D) (PBS: n=21 animals, Bum: n=29 animals; *p<0.05, **p<0.001, ***p<0.0001, two-way ANOVA for A-D).

3.008

ALTERATIONS OF INTRINSIC MEMBRANE PROPERTIES AND EXCITATORY-INHIBITORY TONE IN CA3 PYRAMIDAL NEURONS IN YOUNG ADULT AND AGED FISCHER 344 RATS FOLLOWING SENSORIMOTOR CORTICAL PHOTOTHROMBOSIS

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Rationale: Stroke is the dominant cause of epilepsy in the elderly. Our previous studies using the cortical photothrombosis model of stroke suggest that a higher percentage of aged rats develop limbic seizures after infarction compared to young adults animals.. In order to study the relationship of aging, cortical infarction, and limbic epileptogenesis, we characterized resting membrane potential (RMP) and single action potential (AP) threshold, GABAA receptor (GABAAR)-mediated inhibitory synaptic transmission and AMPA/KA-mediated excitatory synaptic transmission in CA3 pyramidal neurons in control 4 and 20 month old male Fischer 344 rats and one week after infarction.

Methods: AMPA/kainite and GABAAR-mediated whole-cell currents (sIPSCs, mIPSCs, sEPSCs, mEPSCs) were recorded from CA3 pyramidal neurons in transverse dorsal hippocampal slices from 4 and 20 mo old control and lesioned animals with visualized voltage-clamp. RMP and AP measurements were obtained in whole-cell current-clamp mode. Recordings were obtained from the ipsilateral hemisphere of lesioned animals. The covariance of age and infarction on the electrophysiological data were measured with two-way ANOVA. Post-hoc group comparisons were performed with the Bonferonni test.

Results: RMP was depolarized in aged lesioned animals (p=0.006); infarction resulted in a lower AP threshold in both young adult and aged animals (p=0.009). There were no significant effects on sIPSCs, whereas 10-90% rise time of mIPSCs was increased in infarcted animals (p=0.038). Median amplitude of sEPSCs was increased in infarcted animals (0.032), whereas sEPSC frequency was increased by age, infarction, and their interaction (p<0.001). No effects were seen on mEPSCs.

Conclusions: These findings indicate that aging and cortical infarction variably affect intrinsic membrane properties and GABAAR and AMPA/KA functioning in CA3 pyramidal neurons. These plastic changes likely contribute to the increased excitatory tone of the hippocampus following permanent sensorimotor cortical ischemic infarction and predispose it to mechanisms of limbic epileptogenesis.

3.009

ALTERED SYNAPTIC INPUT PRODUCES QUIESCENT INTERNEURONS IN EXPERIMENTAL CORTICAL DYSPLASIA

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Rationale: Cortical dysplasia (CD) is associated with severe epilepsy in humans and we have used in utero irradiation of fetal rats as an injury-based model of CD. These animals show a selective loss of inhibitory interneurons in the affected cortex with a corresponding reduction in synaptic inhibition in pyramidal neurons. Prior studies have shown that surviving fast-spiking interneurons have a reduction in glutamatergic and GABAergic synaptic input; but that the glutamatergic synapses are more severely affected so that there is an imbalance in excitatory-to-inhibitory input that favors inhibition. The current study was undertaken to see how alterations in synaptic input would affect spontaneous action potentials in three types of interneurons in dysplastic cortex.

Methods: Pregnant rats were either sham-irradiated or irradiated with 225 cGy of external X-rays from a linear accelerator source. Coronal slices were obtained from somatosensory cortex at P28-36. We obtained cell-attached recordings from somatostatin (SST)-, parvalbumin (PV)-, and calretinin (CR)-immunoreactive (ir) interneurons in layer IV of controls and the middle region of irradiated animals and quantified spontaneous firing based on frequency and a measure regularity, the co-efficient of variation of the inter-spike interval (CV-ISI). Following cell-attached recordings, the same cells were studied in whole-cell configuration to quantify excitatory and inhibitory post-synaptic currents (EPSCs and IPSCs).

Results: SST- and PV-ir interneurons fired less frequently and with less regularity than controls (Table 1). This corresponded to a relative imbalance in the ratio of EPSCs to IPSCs that favored inhibition (Table 2). In contrast, CR-ir interneurons from CD showed no differences in firing rate or regularity compared to controls. These interneurons showed a normal ratio of EPSCs to IPSCs. Additional studies were performed to examine the effects of pharmacological blockade of glutamatergic and GABAergic transmission on firing rates and regularity. In the presence of glutamatergic and GABAergic blockers, SST- and PV-ir interneurons in CD were no different from controls based on firing rates and CV-ISI.

Conclusions: These findings demonstrate that the relative balance of excitatory and inhibitory synaptic input exerts powerful influence over spontaneous activity of cortical interneurons and that pathological alterations in this balance can impair the normal function of these cells. Specifically, the shift towards predominance of inhibitory input in irradiated rats causes a relative quiescence of SST- and PV-ir interneurons. This may have a significant impact on cortical inhibition in these animals and may be an important mechanism of

epileptogenesis. These same mechanisms may also relevant in some forms of CD-associated epilepsy in humans.

Table 1. Firing Rate and CV-ISI of Interneurons in Control and Dysplastic Cortex

IMAGE: tables/891776_T1.jpg

* P < 0.01

Table 2. Ratio of Frequency and Amplitude of EPSCs to IPSCs of Interneurons in Control and Dysplastic Cortex

IMAGE: tables/891776_T2.jpg

* P < 0.01

3.010

EFFECT OF CENTRAL 5-HT NEURON DELETION ON POST-ICTAL RESPIRATION, SEIZURE-SUSCEPTIBILITY AND SEIZURE-RELATED MORTALITY

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Rationale: Sudden unexplained death in epilepsy (SUDEP) is a devastating condition in which epilepsy patients die for no apparent reason with or without evidence of a recent seizure. Though this has been a long recognized syndrome, the pathophysiology of this disease is not well understood. Both cardiac and respiratory etiologies have been implicated to underlie SUDEP. Serotonin (5-HT) is a key regulator of breathing control, and has been implicated in the pathophysiology of SUDEP. Here we employ a mouse model in which nearly all 5-HT neurons have been genetically deleted to determine whether the absence of 5-HT neurons contributes to seizure-related respiratory dysfunction and death.

Methods: EEG, EMG, EKG, body temperature, locomotor activity and breathing plethysmography were recorded in wildtype (WT) mice and mice lacking 5-HT neurons (*Lmx1b*$^{f/f/p}$) before, during and after seizure induction via either graded pilocarpine treatments (50 mg/kg *i.p.* every 20 min until category 5 seizures attained) or maximal electroshock (10-100 mA, 0.2-0.5 s, 60 Hz sine wave stimulation via ear electrodes).

Results: *Lmx1b*$^{f/f/p}$ mice experienced seizures after lower doses of pilocarpine compared to WT mice (50 mg/kg *i.p. Lmx1b*$^{f/f/p}$; 200 mg/kg *i.p.* WT). *Lmx1b*$^{f/f/p}$ mice also experienced each Racine category of seizure at a shorter latency than WT. Invariably, Category 5 seizures progressed to motor status epilepticus (SE) in all animals of both genotypes. In the post-ictal period following prolonged seizures *Lmx1b*$^{f/f/p}$ mice display profound reduction of respiratory rate and irregularity of respiratory rhythm. All *Lmx1b*$^{f/f/p}$ mice and 50% of WT mice further progressed to death. Only WT mice in which SE resulted in death were included in this analysis. The latency to death from time of first injection was shorter for *Lmx1b*$^{f/f/p}$ compared to WT. Seizures induced by MES were relatively short (15-30 s) in duration and were comprised of a characteristic tonic phase followed by a brief clonic phase and a subsequent period of reduced activity. *Lmx1b*$^{f/f/p}$ mice experienced seizures at lower stimulus intensity (30 mA, 0.2 s, 60 Hz) than WT mice (50 mA, 0.5 s, 60 Hz). In both genotypes, the tonic phase was accompanied by respiratory arrest. Normal breathing spontaneously resumed at the onset of the clonic phase in WT mice. In the majority of *Lmx1b*$^{f/f/p}$ mice, however, breathing did not spontaneously recover and the animals expired. Many *Lmx1b*$^{f/f/p}$ mice did not exhibit clonic activity. Following respiratory arrest and attenuation of the EEG signal resulting from pharmacologically- or electrically-induced seizures, cardiac potentials could be recorded for up to 4 min.

Conclusions: These results demonstrate that elimination of central 5-HT neurons renders mice more susceptible to seizure induction and more prone to seizure-related sudden death. These data further suggest that respiratory mechanisms may be more directly responsible for death than cardiac arrest and that a 5-HT neuron deficit causes post-ictal breathing abnormalities. These findings may have important implications for SUDEP.

3.011

INCREASED INTERCONNECTIVITY BETWEEN HIPPOCAMPAL LAMELLAE MIGHT CONTRIBUTE TO CIRCUITRY HYPEREXCITABILITY IN EXPERIMENTAL TEMPORAL LOBE EPILEPSY

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Rationale: Sprouting and reorganization of hippocampal projections have been demonstrated in human and experimental Temporal Lobe Epilepsy (TLE). Sprouting across hippocampal lamellae has been shown in the mossy fiber projection with new recurrent collaterals into the Dentate Gyrus and the CA3 region using anatomical techniques. Similarly, epileptic sprouting has also been demonstrated in the CA1 axons with new recurrent collaterals into CA1 and across additional lamellae for its projection to Subiculum. We have hypothesized that these anatomical phenomena result in translamellar hyperexcitability (Cavazos and Cross, 2006). We examined this hypothesis with field extracellular physiological techniques in the Kainic Acid (KA) model.

Methods: In-vivo evoked field potentials were recorded from fixed subicular columns 1 wk, 3 wks, or several months after saline (control) or KA injections that induced convulsive status epilepticus (KA groups). SD male rats were monitored to assess the development of spontaneous seizures. Stereotactic recordings were obtained under urethane anethesia using tungsten recording electrodes (0.5MÙ) and Platinum-Iridium bipolar stimulating (intertip distance 0.5mm) electrodes inserted 6.3mm posterior from bregma and 2.5 or 4.5mm lateral from midline, respectively. To optimize the CA1-Subiculum evoked field potential (fEPSP), electrodes were inserted at 20-25 degrees from horizontal plane. Depth of insertions were 4.5mm (recording) and 7.0 ± 0.24mm (stimulation) from the dorsal surface of the brain. After recording spontaneous activity, 0.5ms square wave pulses of 1V were triggered at 2Hz to evoke fEPSPs in Subiculum. fEPSPs were averaged at least for 10 events at each stimulating depth. To determine the functional-topographical organization of the CA1 projection to the Subiculum, we moved the stimulation electrode every 100ìm along dorsal-ventral axis of CA1 pyramidal layer. Animals were prepared for histology to assess location of electrodes and presence of sprouting.

Results: Frequent spontaneous fEPSPs were seen in the Subiculum several months, but not at 1 wk after KA. They were very rare in controls. The dorso-ventral extent of CA1 stimulation that evoked fEPSP in Subiculum was 4.4mm in controls vs 5.9 mm in KA rats. Evoked fEPSPs in Subiculum consisted of three components that evolve in morphology at different depths of CA1 stimulation. There were

progressive alterations in the amplitude, area under the curve, slope and duration of fEPSPs in KA groups as compared to controls. For example, a progressive increase in the maximal duration of Subicular fEPSPs was noted (20.7 ms in controls vs 109.4 ms in KA rats).

Conclusions: Progressive physiological alterations in the hippocampal formation were observed in experimental TLE. There was an increase functional interconnectivity across hippocampal lamellae at the CA1 projection to Subiculum in the KA rat model correlating with progressive increases in sprouting, cellular hyperexcitability and spontaneous seizures.

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3.012

NEW INSIGHTS INTO MECHANISMS OF CRYPTOGENIC INFANTILE SPASMS FROM AN ANIMAL MODEL

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Rationale: Infantile spasms (IS) is a devastating epileptic syndrome of infancy. The hallmarks of the syndrome are clusters of spasms, interictal hypsarrythmia, and progressing mental retardation. Effectiveness of ACTH therapy against IS suggests the involvement of HPA axis as one of the underlying mechanisms of IS. Our group has established the rat model for cryptogenic IS involving prenatal priming with a synthetic glucocorticoid (betamethasone) and postnatal induction of spasms by NMDA. The model shows clusters of NMDA-induced spasms as well as interictal hypsarrythmia-like EEG and ictal EEG electrodecrements, and responsiveness to acute and chronic ACTH treatments. In this study, we focused on corticotropin releasing factor (CRF - a hypothalamic molecule controlling HPA axis), which has been suggested as a candidate molecule in pathophysiology of IS because of its excitatory properties in developing brain, and on methylprednisolone (MPD) - the synthetic corticosteroid with negative feedback on the CRF release.

Methods: Pregnant Sprague-Dawley dams received betamethasone or saline ip injections at G15. The offspring were subjected to NMDA (15 mg/kg ip) on postnatal day (P)15 to induce the flexion spasms.

We tested: (1) Effects of prenatal betamethasone exposure on postnatal expression of CRF in the CNS of P15 pups; (2) Effects of microinfusions (into the hypothalamic arcuate nucleus - Arc or lateral ventricle - LV) or systemic administration (ip) of CRF1 receptor antagonist CP376395 or (3) Effects of acute or chronic pretreatments (ip) with MPD on the prenatally betamethasone primed NMDA-induced spasms.

Results: (1) The expression of CRF in the Arc areas and the paraventricular hypothalamic nucleus (a major source of CRF for the ventral hypothalamus) was increased after prenatal betamethasone priming but before seizures. (2) Administration of CP376395 had region specific effects. Microinfusion of CP376395 in the Arc area delayed initiation of the spasms and decreased their number compared to vehicle infusion, but it had no effect on the spasms when microinfused into the LV or following systemic injection. (3) While the acute treatments with MPD 1h prior to NMDA administration did not affect the spasms, chronic high dose MPD significantly delayed onset of spasms and even significantly decreased the incidence of spasms.

Conclusions: Our results demonstrate the important role of the ventral hypothalamic area (Arc) in the control/modulation of spasms and provide the evidence of disturbances in the CRF regulation in our model of cryptogenic IS. These findings suggest that the CRF system may serve as a potential region-specific therapeutic target for IS.

3.013

ADULT HUMAN NEURONAL PROGENITORS GENERATE FUNCTIONAL NEURONS IN RAT NEOCORTEX

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Rationale: Neurogenesis occurs in adult human brains and adult human neuronal progenitors (AHNPs) have been isolated from surgical specimens. AHNPs can be cultured and expanded in vitro and they can differentiate into cells that are morphologically similar to neurons. An important unanswered question is whether transplanted AHNP-derived neurons are functional and able to integrate into host networks. The present study aimed to answer this question.

Methods: AHNPs were obtained from hippocampal specimens from a 13 year-old female with temporal lobe epilepsy. AHNPs were transduced with rhGFP-lenti viral vectors. They were transplanted into the neocortex of rat pups on postnatal day 1. Whole cell recordings were performed in cortical slices from the rats 17-21 days after transplantation. AHNP-derived neurons were identified using fluorescence microscopy. The firing properties, spontaneous excitatory and inhibitory postsynaptic currents (sEPSCs and sIPSCs) of AHNP-derived (human) pyramidal neurons in layer V were recorded and compared to host (rat) layer V pyramidal neurons.

Results: AHNP-derived neurons in layer V demonstrated regular firing patterns during depolarizing currents and the frequency of firing was not significantly different from host pyramidal cells. The frequencies were 23.67 ± 0.78 Hz for AHNP-derived neurons ($n = 12$) and 23.33 ± 0.86 Hz for host neurons ($n = 10$, $P > 0.1$). Frequency and amplitude of sEPSCs from AHNP-derived and host layer V pyramidal neurons were quantified and compared. There were no differences between the two types of neuron (Table 1). Frequency and amplitude of sIPSCs were also compared and there were no differences between AHNP-derived and host neurons (Table 1).

Conclusions: AHNP-derived neurons in neocortex of rat brain have firing properties similar to host neurons. They receive excitatory and inhibitory synapses from other neurons. The synaptic activities in AHNP-derived neurons are not different from neighboring host neurons. Our results suggest that AHNPs are able to generate functional neurons which integrate into host neuronal networks. This provides promising data on the potential for AHNPs to serve as therapeutic agents in diseases with altered neuronal circuitry such as epilepsy.

Synaptic currents in AHNP-derived and host neurons

3.014

DETECTABLE BLOOD AND BRAIN CONCENTRATIONS OF THE NKCC1 INHIBITOR BUMETANIDE FOLLOWING ANTICONVULSANT DOSES

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Rationale: Hypoxia induced neonatal seizures are often associated with later development of long-term epilepsy, the mechanisms for which are unknown. These seizures are often refractory to conventional GABAergic drugs, thought to be in part due to a developmental overexpression of the chloride (Cl-) co-transporter NKCC1. This overexpression leads to intracellular Cl- accumulation, resulting in a paradoxical Cl- efflux and depolarization in response to GABA channel activation. As in humans, rodent neonatal brain also expresses higher than adult levels of NKCC1 (Dzhala, et al, Nat Med 2005). Bumetanide (BMX), a NKCC1 inhibitor, has been shown to suppress neonatal seizures in the rodent (Dzhala, et al, Ann Neural 2008). We previously reported that 0.15 mg/kg BMX in combination with 15 mg/kg phenobarbital (PB) effectively suppresses hypoxia-induced seizures in postnatal day (P)10 rats. In the present study, we assessed serum and brain concentrations of BMX at the anticonvulsant doses in this seizure model as well as in naïve control litter mates.

Methods: Postnatal day (P)10 rats were pretreated with PB (15 mg/kg) and BMX (0.15 or 0.30 mg/kg), then killed 30 min after graded global hypoxia. Serum and homogenized brain tissue were treated with acetonitrile to precipitate protein. After centrifugation, supernatant was analyzed by LC-MS/MS for BMX quantification (deuterated BMX as the internal standard). In addition, we calculated the ratio of BMX in brain tissue to that in serum.

Results: There was a dose dependent increase in both serum and brain BMX concentrations between the 0.15 and the 0.30 doses (ng/g brain mean: 0.15 dose, 3.50±2.29; 0.30 dose, 4.95±2.24; n=8, p=0.07. ng/ml serum mean: 0.15 dose, 149.4±52.4; 0.30 dose, 294.6±109; n=8, p=0.003). Overall, the mean ratio of brain:serum levels was 0.024±0.015 for the 0.15 dose and 0.018±0.002 for the 0.30 dose (n=8). Interestingly, we found a trend for hypoxic animals having higher concentrations compared to normoxic BMX treated littermate controls (0.15 dose mean: hypoxic, 5.00±2.24; control, 2.00±0.60; n=4, p=0.05. 0.30 dose mean: hypoxic, 6.35±2.49; control, 3.55±0.52; n=4, p=0.07).

Conclusions: Taken together, these data show that anticonvulsant doses of BMX do result in elevated brain and serum levels, suggesting that BMX crosses the blood brain barrier. The trend for higher brain concentrations in animals with seizures suggests that BMX permeability is affected by ictal activity, perhaps due to a break down in the BBB. Finally, these preclinical data help validate the LC-MS/MS for clinical use, as this assay will be used in a clinical pilot study of BMX for neonatal seizures (http://www.clinicaltrials.gov). Supported by P30 HD 18655, 1RC1NS068938-01, the Charles H. Hood Foundation, and the Manton Center.

3.015

EPILEPSY-INDUCED PATHOLOGIC PLASTICITY AND NMDA ALTERATIONS IN THE MALFORMED BRAIN OF HUMAN FCD PATIENTS AND MAM-PILOCARPINE RAT MODEL

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Rationale: Malformations of Cortical Development (MCDs) are developmental brain abnormalities frequently associated with drug resistant focal epilepsy. Among MCDs, type IIB Focal Cortical Dysplasia (FCD IIB) possess distinctive neuro-pathologic and clinical features, and affected patients show severe epilepsy course. To better understand the molecular and cellular mechanisms underscoring the origin and recurrence of seizures in human FCDs, we have undertaken a two-fold approach in both human and experimental settings.

Methods: We have analyzed on one side human pediatric and adult subjects with type IIB FCD surgically treated for drug-resistant focal epilepsy with a combined morphologic and molecular analysis of NMDA receptor complex composition. In addition, we have generated and characterized an experimental "double-hit" animal model by first inducing cortical malformations with prenatal exposure to methylazoxymethanol acetate (MAM) and then triggering, in adulthood, spontaneous recurrent seizures by means of pilocarpine.

Results: Our results on human subjects revealed increased expression of NMDA regulatory subunits in the post-synaptic membranes of dysmorphic neurons, which was evident in both pediatric and adult FCD patients (see Fig 1), thus indicating that abnormalities of NMDA receptor complex are consistently associated with, and may sustain epileptogenesis in FCD IIB patients. The behavioral and EEG data in our experimental model clearly demonstrated higher severity of epilepsy in MAM-pilocarpine (MAM-PILO) than naïve rats made epileptic with pilocarpine. Furthermore, the combined morphologic and molecular analysis demonstrated that chronic epilepsy worsened cortical architectural and NMDA abnormalities induced by MAM administration. Indeed, MAM-PILO rats were characterized by decreased cortical thickness and larger dysplastic pyramidal neurons with recruitment of NMDA regulatory subunits to the post-synaptic membrane, impressively resembling dysmorphic neurons of human FCD IIB (see Fig. 2). The observed abnormalities in chronic epileptic MAM-PILO rats were not due to direct pilocarpine effects or more severe epileptic status. Indeed, FluoroJade and thionine staining demonstrated more widespread cell degeneration and more evident edema in the cerebral cortex of naïve rats treated with pilocarpine alone, thus supporting that cellular/molecular abnormalities observed in the chronic epileptic MAM-PILO rats were determined by the recurrence of seizures.

Conclusions: The present data indicate that in the malformed brain a seizure-induced, cellular/molecular pathologic plasticity may play as a

key actor in establishing a pathological circuitry further affecting the propensity of generating seizures.

IMAGE: images/905499_A.jpg

Fig. 1 NR2B expression in cortical pyramidal neurons of control (A and C) and FCD IIB patients (B, D-F). A-B) ICC staining shows increased NR2B signal in the FCD cortex (B) if compared to control (A). C-F) Confocal images of NR2B IF in control (C) and FCD IIB giant pyramidal neurons. Scale bars: 100 ìm in A-B, 25 ìm in A-B insets and C-F

IMAGE: images/905499_B.jpg

Fig. 2 NMDA over-expression in cortical pyramidal neurons of chronic epileptic MAM-PILO rats. A-B) A clear increase of the NR2AB signal is present in the post-synaptic membranes of cell bodies and apical dendrites (arrows in B) of pyramidal neurons of MAM-PILO as compared to MAM rats (A), with evidence of enlarged spines (arrowhead in B). C-E) Confocal IF staining of NR2AB subunits in rostral (C) and heterotopic (D) neocortex and in the hippocampus (E) of chronic epileptic MAM-PILO rats. Note that the post-synaptic NR2AB up-regulation is associated with the giant pyramidal neurons of heterotopic cortex (D). F-G) Confocal IF of NR2AB (green) - and SMI311 (red) double-labeling (F), and parvalbumin (green) and SMI311 (red) double-labeling (G) in giant dysmorphic neurons of chronic epileptic MAM-PILO rats. The arrowhead in F marks an enlarged dendritic spine. Scale bars: 25 ìm.

3.016

LIPOPOLYSACCHARIDE POTENTIATES HYPERTHERMIA INDUCED SEIZURES: DEVELOPMENT OF A NEW MODEL OF PROLONGED FEBRILE CONVULSIONS

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Rationale: Febrile seizures (FS) are the most prevalent form of early-life seizures, and febrile status epilepticus (FSE) accounts for 25-30% of all childhood SE and over 70% of SE in the first two years of life. While early childhood prolonged febrile convulsions have both acute and long-lasting effects on the developing brain, there is currently no effective therapy. In order to study the role of inflammation and immunity in the development of epilepsy after early-life convulsions, we sought to develop a new febrile convulsion (FCs) model that combines the innate immune activator, lipopolysaccharide (LPS), with hyperthermia-induced seizures to simulate fever from infection.

Methods: P14 Long Evans male rats were injected with LPS (200 ug/kg, i.p.) 2.5 h prior to induction of febrile seizures (30 minute exposure to heated air to maintain core temperature between 38-42oC, modified from Dr. Baram's FS model). Latency to seizure onset, threshold temperature, and total number of seizures were quantified. Controls included hyperthermia alone (FS), LPS alone and normothermic littermates. To show electrographic correlates of behavioral seizures, the prefabricated headmounts (Pinnacle) were implanted (3 FS, 3 FCs (LPS+FS)). At 0.5, 3 or 24 h after FS or FCs, blood and hippocampal tissue were collected for cytokine assay. Rats underwent exploratory behavior or Barnes maze at P21, and latency to KA-induced seizures was measured at P28.

Results: Stable body temperature was maintained in an infant incubator set at 30C until 2.5 h, when slight yet significant rise in temperature was noted in LPS injected pups (36.6±0.1, n=22, vs 37.0±0.1, n=23, $p<0.04$). FCs (LPS+FS) significantly activated IL1-â and TNF-á production in the blood and hippocampus, while hyperthermia seizure (FS) or LPS alone had only modest effects (n=3/group/time). Parallel to an acute increase in cytokine production, LPS primed animals showed a significant decrease in latency to seizure onset (sec) (325.0±16.1, n=22, vs 209.0±17.5, n=23, $p<0.001$), threshold temperature (41.0±0.2 vs 40.0±0.2, $p<0.002$), and an increase in total number of seizures (41±2 vs 63±3, $p<0.001$) compared to FS. EEG confirmed electrographic correlates of seizures manifested by behavioral arrest, hind limb clonus or tonic flexions. The latency to KA-SE at P28 was similarly decreased in animals with prior experience of FS or FCs (83.3±10 (PBS/KA) vs 60.0±5.3 (FS/KA) or 58.4±3.3 (FCs/KA), n=20, $p<0.05$). No behavioral deficits were noted at 7 days after LPS, FS or FCs.

Conclusions: We show that systemic injection of LPS primes the brain to more rapidly respond to hyperthermia and worsening of seizures. After FCs (LPS+FS), but not after FS, cytokines are acutely activated in the blood and brain. Peripheral inflammation appears to work synergistically with hyperthermia to trigger seizures and to exacerbate immune responses. By combining LPS with hyperthermia, we simulated a fever - a regulated increase in body temperature from an immune challenge - and developed a more clinically relevant animal model of prolonged febrile convulsions.

3.017

PLASTICITY IN THE PATHWAY FROM AMYGDALA TO PERIAQUEDUCTAL GRAY (PAG) IS AN IMPORTANT MECHANISM OF EPILEPTOGENESIS IN AUDIOGENIC KINDLING (AK)

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Rationale: The ventrolateral PAG is a brainstem region that is a critical site in the neuronal network for audiogenic seizures (AGS) in genetically epilepsy-prone rats (GEPR-9s). The requisite neuronal network for AGS in GEPR-9s is restricted to brainstem structures, and no forebrain sites are required. Periodic repetition of AGS in GEPR-9s results in AK, which mimics human generalized tonic-clonic seizure in that tonic seizures are followed by generalized post-tonic clonus (PTC). The neuronal network for kindled AGS expands to include forebrain sites, particularly the amygdala, which is a critical site for PTC. Pathways from the amygdala to PAG are well documented. The PTC behavior induced by AK may involve a re-entry of AGS activity from the amygdala to PAG, and the present study examined if changes in this pathway were involved in the mechanisms of epileptogenesis that mediate AK.

Methods: GEPR-9s (200-300 gm) were subjected to the AK paradigm involving 14 AGS (122 dB SPL, re: 0.0002 dyne/cm^2, induced with an electrical bell) over a 7 day period. Under ketamine/xylazine anesthesia a stimulation electrode was implanted in central amygdala and microwire recording electrodes were implanted to record single unit neuronal firing. At least one week after surgery extracellular action potential responses in PAG neurons to electrical stimuli (100-200 µA, 1 msec pulses) in the amygdala were examined in freely moving unanesthetized GEPR-9s. Stimulus response curves were compared in AK and non-kindled GEPR-9s.

Results: PAG neuronal responsiveness to electrical stimuli in the amygdala exhibited increases with increasing stimulus intensity in non-kindled GEPR-9s. However, in GEPR-9s subjected to AK, the firing increase was consistently greater than the levels in non-kindled rats. Thus, in non-kindled GEPR-9s the electrically-evoked action potentials showed a significant increase at 100, 150 and 200 µA. In the GEPR-9s subjected to AK, the mean number of action potentials evoked by amygdala stimulation was greater at all intensities, reaching statistical significance at 150 µA.

Conclusions: The results indicate that consistent PAG neuronal responses were evoked by electrical stimulation in the amygdala, which showed an intensity-related increase in GEPR-9s. GEPR-9s subjected to AK showed greater responsiveness in this pathway, suggesting that AK involves plastic changes in this pathway. This plasticity may be an important mechanism of epileptogenesis that mediates the emergence of PTC induced by AK. (Support: EAM and SIUSM Funds)

3.018

MINOCYCLINE AMELIORATES CEREBRAL LESIONS BUT NOT DECREASES SPONTANEOUS RECURRENT SEIZURES AFTER PILOCARPINE-INDUCED STATUS EPILEPTICUS

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Rationale: Minocycline (MINO) is a broad spectrum tetracycline derived antibiotic with anti-inflammatory properties. It has been shown that MINO could be used as a neuroprotective agent for the treatment of neurological diseases. We examined whether a single dose of MINO administered 2 h after pilocarpine-induced Status Epilepticus (SE) could diminish cerebral lesion and spontaneous recurrent seizures (SRS).

Methods: Adult Sprague Dawley rats were treated with methylscopolamine (2 mg/kg) 30 min before pilocarpine (320 mg/kg) or saline i.p. injection (Control group). All rats were treated with diazepam (10 mg/kg) i.p. 90 min after SE onset. At 20 min after diazepam injection, rats received MINO 25 mg/kg i.p. (SE+Mino group) or saline (SE group). In order to verify cerebral lesions a group of rats were transcardially perfused 5 days after SE induction. Brain sections were processed with Nissl and neuronal nuclei marker (NeuN). The number of NeuN positive cells was estimated using stereology in the piriform cortex (PC). For SRS assessment, rats were video-recorded for approximately 5h per day, beginning 1 week after SE until 30 days later.

Results: Nissl stained sections showed that in SE rats, layer 2 was almost completely ablated in the central and posterior portions of the PC when compared to Control and SE+Mino. Quantification of NeuN labeled cells showed a large neuronal loss in SE rats (n=4; 34,882 ± 5,072; $p<0.05$) compared to Controls (n=4; 96,458 ± 3,057) that was partially recovered in SE+Mino rats (n=4; 54,015 ± 17,920; $p>0.05$). The neuron loss was more robust in layer 2 of the central PC in SE rats (19,734 ± 3,166; $p<0.01$) compared to Controls (64,843 ± 1,554) and this loss was ameliorated in the SE+Mino rats (35,125 ± 12,664). The SE rats presented a decrease of layer 2 volume (0.39 ± 0.05 mm3; $p<0.05$) compared to Controls (0.59 ± 0.05 mm3), that was partially ameliorated by MINO (0.44 ± 0.05 mm3). The analysis of SRS in rats (stage 3 or greater) showed that both SE groups (saline or Mino) presented similar SRS frequency (SE, n=6: 1,15 ± 0,19 SRS/day; SE+Mino, n=5: 1,56 ± 0,33 SRS/day; $p>0.05$).

Conclusions: These results show that MINO administered at a clinically relevant timepoint after SE proved to be neuroprotective, ameliorating neuron loss in the PC, especially in its central portion, a region known to have important influence on seizure development. However, MINO treatment did not prevent the SRS occurrence indicating that it did not prevent epileptogenic progression. Together these data indicate MINO as a neuroprotective drug but higher doses should be tested in order to achieve therapeutic effects.

3.019

ICTAL DEATH IN DRAVET SYNDROME MODEL MICE

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Rationale: Acute unexpected deaths occur frequently in Dravet syndrome (DS). DS model mice, SCN1AR1407X+/- mutant mice, suffer from recurrent spontaneous seizures and 40% of them die within 3 months after birth. SCN1A is reported to be expressed in heart, mainly in sinoatrial node and Purkinje fibers. Thus, we postulate and test the hypothesis that death in DS is related to the channelopathy which commonly affect central nervous system and cardiac conduction system.

Methods: Simultaneous ECG and EEG monitoring were performed in SCN1AR1407X+/- mutant mice: subdural EEG electrodes and two subcutaneous ECG electrodes were implanted in freely roaming mice. Clinical symptoms were recorded by video-monitoring system. We examined effects of hyperthermia in induction of seizures, and applied atropine pretreatment to evaluate the influence of parasympathetic nerve activities on heart.

Results: Ictal deaths were captured in 6 mutant mice; one in spontaneous seizure, and 5 in hyperthermia-induced seizures. In a spontaneous seizure, bradyarrhythmia occured 2.5 sec later after seizure onset, eventually leading to death. In hyperthermia-induced seizures, tachycardia was observed at the beginning of seizures, and thereafter intermittent bradyarrhythmia appeared associated with paroxysmal discharges and characteristic ST changes on EEG (Fig). The intervals from seizure onset to death were 3.0 to 6.5 min (mean 4.7 min). Parasympathetic nerve blockage by atropine pretreatment completely prevented bradyarrhythmia but ST changes remained.

Conclusions: Ictal death in mutant mice occurs following ictal bradyarrhythmia and characteristic ST wave form change, suggesting that common abnormalities of sodium channel exist both in brain and heart. Such phenomena may occur in patients with DS.

IMAGE: images/907464_A.jpg

3.020

OCCURRENCE OF SPONTANEOUS SEIZURE ACTIVITY IN A BILATERAL PRENATAL FREEZE-LESION RAT MODEL

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Rationale: We previously created a novel rat model of focal cortical dysplasia (FCD) using prenatal freeze lesioning. These rats, which had FCD in the left hemisphere, showed vulnerability for developing kindling. However, they lacked spontaneous seizures. In this study, we

created a model with FCD in the bilateral hemispheres and investigated whether this bilateral prenatal freeze-lesion rat model shows spontaneous seizures.

Methods: At 18 days post-conception, a frozen probe was placed on the bilateral scalps of Sprague-Dawley rat embryos, for 4 seconds, through the uterus wall, producing bilateral cortical dysplasia. We also created unilateral freeze-lesion rats (2 points of the lesions). EEG (1 hr/day, 5 days/week, for 6 weeks) recordings were made from both frontal cortices and the hippocampi of postnatal day 42 (P42) bilaterally freeze-lesion (n=9), unilateral freeze-lesion (n=6), and non-freeze-lesion (n=7) rats.

Results: Four bilateral freeze-lesion rats showed spontaneous seizures, which arose from the bilateral hippocampi and evolved to the bilateral hemispheres. Spontaneous seizures were not observed in unilateral freeze-lesion and non-freeze-lesion rats.

Conclusions: Prenatal freeze-lesion rat models might have spontaneous seizures when bilateral cortical dysplasia is produced.

3.021

HUMANIZED MOUSE MODELS OF EPILEPSY

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Rationale: Mutations in voltage-gated sodium channels have been implicated in several types of human epilepsy with varying degrees of clinical severity. Mutations in *SCN1A* were first identified in Generalized Epilepsy with Febrile Seizures Plus (GEFS+), a benign, childhood-onset syndrome in which family members have febrile seizures in childhood and may go on to develop other seizure types as adults. *SCN1A* mutations have also been identified in Dravet Syndrome (Severe Myoclonic Epilepsy of Infancy), an infant-onset syndrome characterized by generalized tonic-clonic or hemiclonic seizures. As the syndrome progresses patients develop other seizure types including myoclonic, absence and partial seizures, and a decline of psychomotor and mental development. More than 700 mutations of *SCN1A* have been reported in patients with epilepsy, making it the most common genetic cause of epilepsy. Functional studies of *SCN1A* mutations in heterologous expression systems have revealed a variety of functional defects. However, there is not an obvious correlation between Nav1.1 dysfunction and severity of the clinical phenotype. The lack of a clear genotype-phenotype correlation may reflect a limitation of *in vitro* expression systems to evaluate neuronal sodium channel mutations. The most reliable data on functional consequences of mutations can be obtained from mice engineered to carry the mutations. However, the resources and time required for generating allelic series of knock-in mice by homologous recombination is prohibitive.

Methods: Recombination-mediated cassette exchange (RMCE) allows for rapid and efficient production of an allele series of mice carrying mutant DNAs at the target locus. In this method, a cassette acceptor containing a selectable marker flanked by lox sites is targeted to the endogenous mouse locus by homologous recombination. Subsequent exchange of the cassette acceptor for the sequence of interest occurs by cre-mediated recombination in the ES cells, which is much more efficient than homologous recombination. The gain in efficiency decreases the time and resources required to generate multiple variants, allowing for parallel generation of an allelic series of mice.

Results: We generated a mouse ES cell line in which *Scn1a* exon 1 containing the translation start site was replaced by a loxed cassette acceptor via homologous recombination. Subsequent exchange with *SCN1A* cDNAs allows expression of the human cDNA under the endogenous regulatory control while ablating expression of the mouse gene.

Conclusions: This approach will enable *in vivo* characterization of human epilepsy mutations and provides a valuable resource for understanding the mechanisms underlying epilepsy and developing novel therapeutic strategies.

3.022

THALAMIC KINDLING IN RATS WITH GENETIC ABSENCE EPILEPSY

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Rationale: Genetic absence rat strains are resistant to generalization of kindling seizures induced by limbic stimulation. These observations raise the question whether the resistance is universal and independent of the stimulation site or whether it is related to the structures stimulated. Midline thalamic nuclei have been implicated as a critical region for the generalization of kindled limbic seizures. We compared kindling of the hippocampus and the midline thalamic nuclei in Sprague Dawley and WAG/Rij rats to determine whether kindling resistance was circuit specific.

Methods: Following the implantation of a unilateral hippocampal, mediodorsal thalamus and frontal cortical electrodes, rats were kindled in either the hippocampus or midline thalamus until they were fully kindled or had received 50 stimulations. We evaluated the progression of the after discharge and behavioral seizure severity (Racine Scale).

Results: Compared to Sprague-Dawley rats, the WAG/Rij animals with well developed spike wave discharges never fully kindled with hippocampal stimulation. In contrast both groups kindled rapidly with thalamic stimulation with many fewer stimulations compared to hippocampal stimulation. For the Sprague-Dawley rats, the mean number of stimulations for kindling was 21.6±4.15 (Mean±SEM) for the hippocampus and 3.2±1.7 for the thalamus. In comparison WAG/Rij rats were not kindled after 50 stimulations but were kindled after 6.9±2.1 thalamic stimulations. Mean durations of the first thalamically induced afterdischarge were 15.1±1.7 and 12.1±1.5 seconds, respectively.

Conclusions: Whereas WAG/Rijs are resistant to hippocampal kindling, they rapidly develop motor seizures with thalamic kindling. These findings suggest that resistance to generalization in WAG/Rij rats may arise from the inability to access networks for generalization from the limbic structures rather than complete resistance to generalization.

3.023

DEFICITS IN MEMORY AND SOCIAL BEHAVIOR FOLLOWING SEIZURES EARLY IN LIFE

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Rationale: One of the most devastating aspects of developmental epilepsy is the long-term impact on cognitive behavior. In addition, children with epilepsy show a high co-morbidity with psychiatric disorders and autism spectrum disorder (ASD). One of the critical

determinants of a child's behavioral outcome in autistic spectrum disorder and cognitive behavior is the age of onset of seizures.

Methods: In order to examine whether early-life seizures result in learning and memory deficits and behavioral features of ASD we administered the inhalant fluorothyl to induce seizures in C57BL/6 mice. The mice received three seizures per day for five days starting on postnatal day 7. The parallel control groups consisted of similarly handled animals that were not exposed to fluorothyl, and naïve mice. Male and female mice were both included to examine whether there was a sex-specific effect of early-life seizures on behavior. The subjects were then processed through a battery of behavioral tests in adulthood: open field activity, elevated-plus maze, nose-poke assay, marble burying, social partition, social chamber, and Morris water maze.

Results: The mice with early-life seizures had learning and memory deficits in the training portion of the Morris water maze ($p < 0.05$) and probe trial ($p < 0.01$). The mice with seizures showed no differences in marble burying, nose-poke assay, open-field or plus-maze testing compared to controls. However, they showed a significant difference in the social chamber and social partition tests. Mice with early-life seizures showed a significant decrease in the total time they spent at the cup with the other mice ($p < 0.01$) and showed no preference in the mean interaction time with the cage containing the mouse than with the novel object, while the control mice showed a significant preference for the cage with the mouse ($p < 0.01$). These results were similar in male and female mice. However, male mice with prior seizures did not show an increase preference to the novel mouse in the social partition test compared to the control male mice. Both social behavior tests suggest that early-life seizures result in severe disruptions in social behavior.

Conclusions: These results indicate that early-life seizures result in deficits in hippocampal-dependent memory tasks and produce long-term disruptions in social behavior.

3.024

MINOCYCLINE REVERSES ANHEDONIA IN AN ANIMAL MODEL OF COMORBIDITY BETWEEN EPILEPSY AND DEPRESSION

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Rationale: Post-status epilepticus (SE) chronic epilepsy in rats has been validated as a model of comorbidity between epilepsy and depression by behavioral, biochemical and neuroendocrine assays. Activation of an inflammatory cytokine interleukin-1â in the hippocampus has been suggested as a mechanism of epilepsy-associated depression (Mazarati et al., Neurobiol. Dis. 2010; 37:461-467). Another hallmark of neuroinflammation - microglia activation - has been implicated both in post-SE epilepsy and in major depression. We studied whether a microglia inhibitor minocycline (MINO) would exhibit antidepressant and anticonvulsant effects in post-SE rats.

Methods: Two months after LiCl-pilocarpine SE, adult Wistar rats were examined for the presence of symptoms of depression: dysregulation of hypothalamo-pituitary-adrenocortical (HPA) axis using dexamethasone (DEX)-corticotropin releasing hormone (CRH) test coupled with plasma corticosterone (CORT) radioimmunoassay; despair using forced swim test (FST); anhedonia using taste preference saccharin consumption test. MINO (50 mg/kg/day) was administered for 10 days. Animals were monitored for spontaneous seizures for 10 days prior to, and throughout MINO treatment. At the end of MINO regimen, tests for depression were repeated.

Results: Post-SE rats exhibited depression-like impairments. Dysregulation of HPA axis was evident as the decrease of CORT level (81% of that in controls); failure of DEX to suppress CORT (post-DEX/pre-DEX CORT levels were 78% post-SE and 34% in controls); exacerbated response to CRH (post-CRH/pre-CRH CORT levels were 620% post-SE and 315% in controls). Despair was evident as the increased immobility time in the FST (59% of total swimming time post-SE vs. 27% in controls, $p<0.05$). Anhedonia was revealed by the absence of preferential consumption of saccharin solution versus tap water (saccharin/saccharin+water consumption was 48% post-SE and 78% in controls). Treatment with MINO reversed anhedonia (saccharin consumption was 73% of total fluid, $p<0.05$ vs. before MINO, $p>0.05$ vs. controls). MINO improved neither behavioral deficit in the FST, nor the dysregulation of HPA axis. Minimal-maximal-median seizure number over ten days was 2-9-6 prior to, and 1-11-4.5 during MINO regimen ($p>0.05$).

Conclusions: In the post-SE model of comorbidity between epilepsy and depression MINO exerted therapeutic effect on anhedonia, but not on despair, dysregulation of HPA axis, and spontaneous seizures. The effect of MINO was different from that previously established for interleukin-1 receptor antagonist which improved all symptoms of depression. Lack of an effect of MINO on the FST contrasted with its effectiveness in models of major depression; this suggests mechanistic differences between major depression and depression as a comorbidity of epilepsy. Upon further validation, MINO may be beneficial in patients with epilepsy and concurrent depression in whom anhedonia represents a leading mood impairment.

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3.025

ELECTROPHYSIOLOGICAL INVESTIGATION OF HIPPOCAMPAL NEUROGENESIS INDUCED BY EPILEPSY

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Rationale: Neuronal regeneration is thought to be induced by stimulation from ischemia or epileptic seizures, as well as to compensate for neuronal necrosis or apoptosis from such insults. It is also said that neuronal regeneration is a cause of hippocampal epileptogenesis, although much is unknown about the turnover mechanism or significance of newly formed neurons. Using an animal model in which epileptic seizures were induced by pilocarpine, changes in hippocampal neurogenesis with time brought about by epilepsy were investigated using immunostaining and electrophysiological (patch-clamp) techniques. The role of hippocampal neurogenesis in epileptogenesis was then examined.

Methods: Twenty-four hours after epileptic seizures were induced by intraperitoneal injection of pilocarpine in C57/BL mice, the hippocampus was injected with a green fluorescent protein (GFP) using a retrovirus. Thus, new nerves induced by the epileptic seizure were marked with GFP. Immunostaining was done 7 days (1 week), 14 days (2 weeks), and 28 days (4 weeks) after status epilepticus, and the degree of maturation of normal neurons (NeuN staining) and the proportion of apoptosis (ssDNA staining) were investigated. With the patch-clamp, the firing pattern in the cells marked with GFP was directly recorded to investigate cell excitability.

Results: Many new cells were produced in the subgranule zone after the epileptic seizures, but they were small and fragile, and almost none of the immature GFP-positive cells entered the maturation process. They disappeared by 1-4 weeks after the seizure. The GFP-positive cells that disappeared at an early stage were negative for both ssDNA and NeuN. The GFP-positive cells at 1-2 weeks after the seizure had input resistances (IRs) of 1.2 GÙ-2.0 GÙ and resting membrane potentials (RMPs) of "55 mV to "70 mV. The GFP-positive cells at 4 weeks had IRs of 300 MÙ-1000 MÙ and RMPs of "70 mV to "80 mV.

Conclusions: The membrane resistance in the new neurons induced by epilepsy was higher in the less mature cells, and they had a low firing rate.

IMAGE: images/887055_A.jpg

3.026

MECHANISM-BASED COMBINATION DRUG THERAPY IN A MOUSE MODEL OF SEVERE MYOCLONIC EPILEPSY IN INFANCY

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Rationale: Severe Myoclonic Epilepsy in Infancy (SMEI, Dravet syndrome) is associated with loss of function in the Nav1.1 voltage-gated sodium channel, a brain specific channel important for neuronal excitability. Seizures begin at 6-9 months typically associated with elevated body temperature or fever. Later spontaneous seizures and status epilepticus are associated with cognitive and motor decline. Current therapies are ineffective. We developed a mouse model of SMEI (mSMEI) by targeted disruption of Scn1a which recapitulates the spontaneous and thermally induced seizures of SMEI. mSMEI have reduced sodium current in GABAergic inhibitory interneurons but not excitatory cells resulting in selective failure of firing of GABAergic neurons. This dysfunction is the likely cause of seizures and co-morbidities in mSMEI. We hypothesize that combinations of drugs that enhance GABAergic neurotransmission by complementary mecha¬nisms will be efficacious in compensating for the selective reduction of firing of GABAergic interneurons. . In this study, protection against thermally induced seizures was determined for two drugs that enhance GABAergic neurotransmission, tiagabine (TGB) a presynaptic GABA reuptake inhibitor and clonazepam (CLN), a postsynaptic allosteric modulator of the GABA-A receptor.

Methods: 30 minutes after i.p. injection, body core temperature was elevated from 36.5 °C to 42.5 °C or until a generalized tonic-clonic (GTC) seizure. Myoclonic (MC) seizures were seen preceding GTC seizures. The difference in body core temperature at seizure onset between treated and untreated mSMEI was determined. Dose-effect relationships were determined by Hill fits. Isobolographic analysis was used to determine antagonism, additivity, or synergy when the drugs were given in combination.

Results: Untreated mSMEI had MC seizures at an average body temperature of 38.2 °C and GTC seizures at 38.4 °C. The maximal protective effect was greater for CLN than TGB (3.6±0.2 °C vs 1.4±0.3 °C respectively for MC seizures and 4.1±0.08 °C vs 3.1±0.2 °C for GTC seizures). The half maximal protective dose was lower for CLN than TGB (0.1±0.03 mg/kg vs 0.4±0.2 mg/kg for MC seizures and 0.1±0.01 vs 0.5±0.08 mg/kg for GTC seizures). Above 0.3 mg/kg, TGB increased the number of MC seizures seen before GTC from 7.5±1.4 in untreated mSMEI up to 348±29 at 40 mg/kg. MC seizures were not increased with CLN. Combined doses of CLN and TGB tested at 1:1 and 1:3 fixed dose ratios, showed additive efficacy using isobolographic analysis without an increase in MC seizures.

Conclusions: GABA-acting antiepileptic drugs CLN and TGB protect against thermally-induced seizures in mSMEI. TGB was associated with a substantial increase in MC seizures at higher doses, a significant toxicity. Combined therapy with CLN and TGB was additive without an increase in MC seizures. Combinations of GABA-acting drugs with complementary mechanisms of action result in additive efficacy with reduced toxicity in a mouse model of SMEI.

3.027

TREATMENT WITH LACOSAMIDE IMPEDES GENERALIZED SEIZURES IN RODENT MODEL OF CORTICAL DYSPLASIA

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Rationale: The new antiepileptic medication Lacosamide (LCM) has been shown to be effective in various animal epilepsy models. Its efficacy is demonstrated in clinical trials for partial-onset seizures as adjunctive therapy. In contrast, there is only indirect evidence for efficacy in animal models of generalized epilepsy. To further explore the potential effects of LCM in rodents we completed a preliminary series of experiments utilizing an established animal model for symptomatic epilepsy, whereby a pro-epileptic substrate of multifocal cortical dysplasia is induced via in utero irradiation. Adult rats are known to exhibit seizures following a single subconvulsive dose of PTZ injection. Thus, we measured the effect of LCM on seizure activity provoked by a systemic PTZ injection in these animals.

Methods: Following a standard protocol that has been developed and utilized in our laboratory, 13 Sprague-Dawley rats were divided into 4 experimental groups: 1)-XRT/-LCM (n=4); 2)-XRT/+LCM (n=4); 3)+XRT/-LCM (n=2) ;4)+XRT/+LCM (n=3).

Five rats were irradiated with 145cGy in utero on E17 (XRT; "first hit").All rats were implanted with epidural electrodes on PND 55. On PND 60 rats were given a single dose of LCM (25mg/kg i.p.) 30 minutes before receiving a single subconvulsive dose (40 mg/kg s.c.) of pentylenetetrazol (PTZ; "second hit"). Their behavior and EEG were monitored for a subsequent 8 hours. Seizure severity was assessed using a standard scale (Veliskova et al. 1989).

Results: All control animals (-XRT/±LCM) had less severe seizures (Grade1 n=7; Grade 2 n=2) as compared to XRT animals. The two untreated irradiated animals (+XRT/-LCM) had severe generalized seizures (Grade 4). Treated irradiated animals (+XRT/+LCM) were observed to have less severe seizures (Grade 1, 2, 3, n=1 respectively).

Interestingly the ictal EEG analyses showed that the frequency of spike wave complexes during generalized seizures was lower (~4-5Hz) in animals treated with LCM, as compared to untreated animals (~6-7Hz) regardless of XRT allocation.

Conclusions: Treatment with LCM impedes acute generalized convulsive seizures induced by a "2nd hit" in a rat model of in utero radiation induced cortical dysplasia. These experiments are ongoing. If confirmed, this preliminary data would suggest that LCM may be effective in some (symptomatic) generalized seizures. Comparisons with other sodium channel blockers (such as CBZ) are also under way in our laboratory.

3.028

FUNCTIONAL STUDIES OF INTERLEUKIN 1-BETA IN THE PILOCARPINE RAT MODEL OF EPILEPSY USING RNA INTERFERENCE

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Rationale: The aim of our study was to investigate the role of interleukin1-beta (il1b) in the pilocarpine rat model using RNA interference as a functional tool.

Methods: Small interfering RNA molecules (siRNA) targeting the interleukin-1b gene (il1b) and and its endogenous antagonist (il1ra) were conjugated with a glycoprotein derived from the rabies virus (RVG-9R) to ensure optimal delivery into the central nervous system. Eight-week-old male rats were divided into four groups: i) a control group injected with buffer; ii) a second control group injected with an irrelevant siRNA; and iii) and iv) two experimental groups injected with siRNA directed against the two target genes (il1b and il1ra). SiRNA complexes were delivered by intravenous injection in the caudal vein. Intravenous injections were performed 48 h prior to induction of the pilocarpine model.

Results: Transvascular delivery of siIl1b and siIl1ra promoted significant gene silencing in the brain 48h post-injection (p.i.), with the highest silencing effect observed at 72h p.i. SiRNA injections provided a dose-response curve, and successful gene knockdown was achieved in four out of five brain regions analyzed. In addition, no evidence of off-target gene effects was observed and gadolinium-MRI showed no disruption of the blood-brain-barrier after the siRNA injections. Phenotypic analysis of the animals which had il1-b silenced showed a significant decrease in the latency for the first seizure ($p<0.05$) as well as for the status epilepticus (SE) ($p<0.05$). In contrast, the animals which had il1ra silenced (il1-b endogenous antagonist) had a significant increase in latency for the first seizure ($p<0.05$) as well as for SE ($p<0.05$). Furthermore, we found that by silencing il1b a down-regulation of Slc1a3 was also obtained. Slc1a3 is one of the most important transporter proteins involved in glutamate re-uptake in the synaptic cleft. In addition, histological analysis of tissue obtained from animals in the chronic phase showed a significant decrease in neuronal cell death in the hippocampus of animals which had been previously silenced for il1ra (il1\b endogenous antagonist).

Conclusions: Our results indicate that il1b may have a protective effect in the early stages of the pilocarpine rat model. In addition, this effect seems to be mediated by glutamate regulation in the synaptic cleft.

3.029

PENTYLENETETRAZOLE INDUCED NEONATAL SEIZURES IN TRANSGENIC KNOCK-IN MICE LACKING GLUR1 PHOSPHORYLATION REVEAL CRITICAL ROLE OF AMPA PHOSPHORYLATION IN EPILEPTOGENESIS

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Rationale: Neonatal seizures (NS) have been shown to contribute to severe long-term effects including epilepsy, cognitive impairment, mental retardation and behavioral deficits. We have previously shown that early alterations in protein kinase activity and enhanced phosphorylation of the AMPA receptors at GluR1S831 andGluR1S845 play a critical role in mediating the hyperexcitability and epileptogenesis following NS in the rat (Rakhade SN et al, J Neurosci. 2008). We hypothesized that eliminating the phosphorylation of GluR1 receptors will attenuate the epileptogenesis following neonatal seizures. To unambiguously determine the role of these phosphorylation sites in seizures, we compared seizure thresholds/latencies between GluR1 phosphomutant mice (GluR1 DPM -/-) and their wild-type littermates (GluR1 DPM +/+).

Methods: GluR1 phosphomutant mice (GluR1 DPM -/-) and their wild-type siblings (GluR1 DPM +/+) were obtained by mating heterozygous mice as described previously (Cell. 2003 Mar 7; 112(5):631-43.). Pentylenetetrazol (PTZ, 50 mg/kg i.p.) was used to induce generalized tonic-clonic seizures at postnatal day 7. Seizures were recorded and latency to behavioral seizures calculated. Hippocampal slices obtained from the GluR1 DPM -/- mice and their wild-type siblings at P7 and subjected to hypoxic conditions, single cell patch clamp recordings were made as described previously (J Neurosci. 200525(13):3442-51.) The degree of phosphorylation of the GluR1 reecptor subtype in the hippocampus and cortex were analyzed by immunoblotting.

Results: Transgenic knock-in mice with mutations in GluR1 phosphorylation sites S831 and S845 have been shown to have deficits in LTP, LTD and spatial memory tasks (Lee HK et al, Cell ,2003 Mar 7;112(5):631-43). GluR1 DPM -/- mice exhibit an increased latency to onset of first behavioral seizure following PTZ injection (6.54 min ± 0.75, $p<0.005$, $n=23$) as compared to wild-type littermates subjected to same conditions (3.75 min ± 0.39). Wild-type mice subjected to PTZ induced neonatal seizures at post-natal day (P) 7 exhibit an increase in the phosphorylation of GluR1 Ser 831 (128 %, $n=4$) and GluR1 Ser 845 (134%, $n=4$, $p<0.05$) at 1 day following seizures s. There is a significant increase in expression of PSD-95 (192%, $n=6$, $p<0.05$) at 24 hours after induction of PTZ seizures, compared to littermate controls.

Conclusions: These data suggest that GluR1 DPM -/- mice exhibit less excitability and are less prone to synaptic potentiation following neonatal seizures as compared to wild type littermate controls. The attenuated response to PTZ and the lack of neuronal hyperexcitability in area CA1 in GluR1 DPM transgenic mice supports the hypothesis that phosphorylation of the GluR1 receptor subunit is an early and critical step in the process of epileptogenesis following early life seizures. Furthermore, the phosphorylation event may be targeted as a potential antiepileptogenic target for preventing the long-term consequences of early life seizures.

3.030

THE INTERACTIONS OF INTERLEUKIN-18 AND INTERFERON-ã ON THE NEUROPROTECTION IN THE RAT HIPPOCAMPUS FOLLOWING STATUS EPILEPTICUS

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Rationale: Although Interleukin-18 (IL-18) and interferon-ã (IFN-ã) are involved in inflammatory responses under neuropathological conditions, the role of IL-18 and IFN-ã in epilepsy is still controversial.

Methods: To elucidate whether IL-18 participates in epilepsy-related events, we investigated the changes in IL-18 and INF-ã systems within the rat hippocampus following status epilepticus (SE)

Results: : In non-SE induced animals, IL-18, IL-18 receptor á (IL-18Rá), IL-18 binding protein (IL-18BP), IFN-ã and IFN-ã receptor á (IFN-ãRá) immunoreactivity was not detected in the hippocampus. Following SE, IL-18 immunoreactivity was increased in CA1-3 pyramidal cells as well as dentate granule cells. IL-18 immunoreactivity was also up-regulated in astrocytes and microglia. IL-18Rá immunoreactivity was detected in astrocytes and microglia. IL-18BP immunoreactivity appeared in astrocytes and microglia. IFN-ã immunoreactivity was detected only in astrocytes within all regions of the hippocampus. IFN-ãRá immunoreactivity was increased in neurons as well as astrocytes. Intracerebroventricular infusions of recombinant rat IL-18 or INF-ã alleviated SE-induced neuronal damages, while neutralization of IL-18, INF-ã or their receptors aggravated them, as compared to saline-infused animals.

Conclusions: These findings suggest that astroglial-mediated INF-ã pathway in response to IL-18 induction may play an important role in alleviation of SE-induced neuronal damages.

3.031

CIRCADIAN RHYTHM OF CORE BODY TEMPERATURE IN AN ANIMAL MODEL OF CHRONIC EPILEPSY

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Rationale: The relationship between circadian rhythm and epilepsy is poorly understood although circadian periodicity in the occurrence of seizures has been recognized for more than a century. Recent work by our group (Talathi et al Neurosci. Lett.,15:455, 2009; Fisher et al, Biol. Cybern., epub ahead of print 2010) has shed some light on the circadian phase dependent modulation in the excitability of hippocampus in an animal model of chronic epilepsy. In order to further elucidate the relationship between hippocampal excitability and the endogenous circadian rhythm in an epileptic brain, we have focused on systematic investigation of the alterations in the circadian activity in relation to spontaneous seizures in an animal model of chronic epilepsy. Here we report preliminary findings of the changes in the circadian rhythm of the core body temperature (CBT) in an animal model of chronic epilepsy.

Methods: Male Sprague-Dawley rats (n=2) weighing ~265 g were implanted with an RF transponder in the abdominal cavity and a stimulating electrode in the ventral hippocampus. Following recovery the rats were transferred to controlled 24 h LD environment. The CBT was continuously monitored. After baseline recordings, the rats were brain injured through electrical stimulation. The CBT rhythm of rats with injured brains was monitored for 4 weeks in 24 h LD cycle. During this time period the rats exhibited spontaneous seizures. The rats were then moved to 24 DD (constant routine) environment and monitored for four additional weeks. The Lomb Scargle periodogram was used to estimate the period of statistically significant oscillations in the circadian range.

Results: Following injury, after a transient period of 4-5 days, the mean CBT rose by 0.23+0.07 oC and the period of circadian rhythm decreased by 0.3+0.01 h. The phase of CBT oscillation shifted by -1.38+0.003 h. After the rats were transfered to 24 DD routine, the mean CBT returned to baseline, however the CBT free-ran with endogenous period of 24.46+0.007 h. The phase was observed to be shifted to 0.95+0.6 h. In addition a statistically significant peak ($p<0.05$) at ~12 h was observed in the Lomb Scargle periodogram. The occurrence of spontaneous seizures did not have any observable effect on the rhythm of CBT.

Conclusions: Brain injury transiently disturbs the circadian rhythm of CBT and the rhythm appears to be desynchronized from the LD cycle with period less than the imposed 24 h period. In addition, statistically significant peak in CBT rhythm at ~12 h is observed in epileptic rats under constant routine protocol. We hypothesize that ~12 h harmonic in the periodogram of CBT rhythm, which is unmasked in the constant routine protocol, is induced by seizures. This harmonic in turn shifts the phase of the CBT rhythm, and in turn may be associated with hyperexcitability observed in an epileptic brain

Core Body Temperature Statistics

IMAGE: tables/910118_T1.jpg

*: Statistically significant difference from baseline (Prestim L/D)

3.032

CCL2 IS RAPIDLY INCREASED IN PIRIFORM CORTEX, HIPPOCAMPUS, AND NEOCORTEX BUT NOT IN CEREBELLUM AFTER PILOCARPINE-INDUCED SEIZURES

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Rationale: Cytokines and nervous tissue inflammation has been shown to play a role in epileptogenesis. In this work the concentration of Interleukin 1-beta (IL-1â), C-C motif ligand 2 chemokine (CCL2), and Tumor Necrosis Factor-alpha (TNF-á) were measured in rats piriform cortex, hippocampus, neocortex, and cerebellum following status epilepticus (SE) induced by pilocarpine injection.

Methods: Adult Sprague Dawley rats were treated with methylscopolamine (2 mg/kg) 30 min before pilocarpine i.p. injection (320 mg/kg). Ninety minutes after SE onset rats received diazepam (10 mg/kg). Control rats were injected with saline instead of pilocarpine. Animals were deeply anesthetized and decapitated 2h, 6h, 24h or five days (n=12 per timepoint) after diazepam treatment. The brain was quickly removed and the piriform cortex, hippocampus, neocortex and cerebellum were dissected and immediately frozen in liquid nitrogen.

Cytokines tissue levels were assayed in tissue homogenates against a standard curve provided by the Milliplex MAP kit (Millipore). The fluorescence intensity was measured on the Luminex machine (Millipore) and the analyte concentration was determined using the BioRad software (BioPlex Manager). The assay was run in triplicate to confirm the results. The tissue concentration of the cytokines were normalized to the total protein concentration and presented as pg/ìg of total protein ± SEM.

Results: An example of the measured CCL2 concentrations in the piriform cortex, hippocampus, neocortes, and cerebellum can be observed in Figure 1. A large increase was observed in all time points. An increase of 3-4 times the basal levels ($p<0.001$) was already observed 2h after SE and this increase peaked 24h after SE with a ~100 fold increase in the hippocampus and ~200 fold increase in the piriform cortex ($p<0.001$ in both cases). A similar profile was observed in the neocortex but no significant alterations were observed in the cerebellum. Smaller increases were observed in IL-1â levels and no significant alterations of TNF-á.

Conclusions: The large increase of CCL2 concentration on limbic and cortical structures involved with the later progression of spontaneous seizures and the absence of such alteration in the cerebellum indicate an important role for this chemokine in epileptogenesis. This chemokine can also be employed as a biological marker for inflammation of the nervous tissue.

IMAGE: images/874780_A.jpg

Chemokine CCL2 concentration in the brain regions analyzed at different timepoints after SE. Note the log scale in the vertical axis. $p<0.001$ in all timepoints for piriform, hippocampus and neocortex SE animals.

3.033

COMPARISON OF TWO SEIZURE THRESHOLD RAT MODELS FOR EVALUATION OF PROCONVULSANT DRUG PROPERTIES

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Rationale: Safety pharmacology studies often include experiments on seizure threshold in rodents for detection of proconvulsant drug activity. Therefore, reliable identification of proconvulsant drug activity by preclinical models is of particular importance. The timed intravenous (i.v.) pentylenetetrazole (PTZ) infusion seizure test is used as a standard model for preclinical assessment of proconvulsant drug activity. However, it has been revealed that substances, which show proconvulsant effects in the PTZ test, may have the opposite effect on electrical seizure thresholds. To address this point, we compared effects of several substances, including both anti- and proconvulsant drugs, on seizure thresholds in the timed i.v. PTZ infusion test with those elicited in the maximal electroshock seizure threshold (MEST) test.

Methods: In freely moving adult male Wistar-Unilever rats PTZ was infused at a concentration of 0.8% at 1 ml/min via the tail vein. The threshold to induce a first myoclonic twitch or a clonic seizure in mg/kg PTZ infused was determined following vehicle treatment, and threshold determination was repeated 2-3 days later 30 minutes after intraperitoneal injection of one of the following drugs: phenobarbital, 20 mg/kg; d-amphetamine, 5 mg/kg; chlorpromazine, 3 mg/kg; theophylline, 30 and 50 mg/kg; caffeine, 60 and 80 mg/kg; or of tramadol, 2.5; 5, 10, and 20 mg/kg. Each rat served as its own control; 3-8 rats were used per experiment. For the MEST test, the same doses and pretreatment time were used to record the CC50, i.e. the convulsive current needed to induce either a forelimb or hindlimb tonus following current application via corneal electrodes in 50% of the animals, using 14-24 rats per MEST determination. In addition, latency to and duration of seizure endpoints as well as mortality were recorded.

Results: Phenobarbital was shown to enhance seizure thresholds for recorded endpoints in both the PTZ test as well as the MEST test. In contrast, the known proconvulsant drug d-amphetamine significantly decreased PTZ seizure threshold whereas it increased the CC50 in the MEST test. Similarly, chlorpromazine exhibited a proconvulsant effect in the PTZ test, whereas we observed no influence on MEST seizure threshold. Interestingly, with caffeine and theophylline, we found no proconvulsant effects in the PTZ test, but theophylline even increased seizure threshold for myoclonic twitch. On the contrary, methylxanthines dose-dependently lowered seizure threshold in the MEST test. At 2.5 mg/kg, the opioid tramadol did not alter seizure threshold in both models. However, at higher doses, it significantly decreased seizure thresholds in the PTZ test, whereas it exerted anticonvulsant effects in the MEST test.

Conclusions: Despite the fact that both seizure threshold models are suitable to detect proconvulsant drug activity, results are not always consistent. Thus, the sole use of one test to assess the proconvulsant potential of a substance during drug development is not sufficient as it may lead to false negative or positive conclusions.

3.034

SPONTANEOUS INFANTILE SPASM-LIKE EVENTS PROVOKED BY CHONIC EARLY LIFE STRESS: A NEW MODEL OF IDIOPATHIC INFANTILE SPASMS THAT EXPLAINS THE EFFICACY OF ACTH?

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Rationale: Infantile spasms (IS), a catastrophic, age-dependent epilepsy, are provoked by numerous etiologies and are abolished by high doses of ACTH. However, how these many etiologies induce the spasms, and why IS respond to the stress hormone ACTH is unclear. We previously found that children with IS have abnormal stress-hormoned levels in CSF (Baram et al., 1992, 1995), and that in rodents, ACTH suppressed brain levels of the stress hormone CRH (Brunson et al.,2001). CRH expression is increased in several brain regions by severe stress, and induces seizures in immature rodents (Baram and Hatalski, 1998). Taken together, these finding predict that early life stress (perhaps a common denominator of developmental problems associated with IS) will increase brain excitability and result in spontaneous IS via CRH-mediated mechanisms.

Methods: To test this hypothesis, we induced chronic stress in neonatal rats on postnatal (P) day 2-9, using a simulated poverty paradigm (limiting maternal nesting material; Brunson et al., 2005). Rats (n = 12) were implanted with hippocampal or amygdala electrodes on P11-15, and video-EEG obtained between days P14-P36. Unstressed, normally reared control rats (n = 5) underwent the same video-EEG procedures.

Results: Abnormal flexion spasms, singly and in clusters, were observed in 5/12 stressed rats and in none of the controls. These commenced on postnatal day 16 and disappeared by day 35. One additional stressed rat developed two limbic seizures that generalized. EEG correlates of the spontaneous flexion spasms were obscured by

cable artefact (in 3), and consisted of a spike followed by voltage attenuation (in 2). Additional abnormal myoclonic events, associated with spike / attenuation on EEG, were noted throughout the recording period in 6/12 rats.

Conclusions: EEG in otherwise normal rats. These finding support the idea that a common denominator of the many IS etiologies is activation of the brain's stress system, and increased expression and release of CRH, an excitatory neuropeptide that causes seizures. In this scenario, the mechanism of action of ACTH in ameliorating IS, includes suppression of CRH expression, as shown in rodents (Brunson et al., 2001). Stress-induced spontaneous spasms in infant rats reproduces many of the features of idiopathic/ cryptogenic infantile spasms and should provide a useful model for mechanistic and therapeutic studies.

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3.035

A BLIND RANDOMIZED STUDY OF ANTI-EPILEPTIC AND ANTI-EPILEPTOGENIC EFFECTS OF CARISBAMATE ON POSTTRAUMATIC EPILEPSY IN THE RAT

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Rationale: Carisbamate (CRS) is an antiepileptic that progressed to phase III clinical trials. It has a broad spectrum of activity in conventional preclinical anticonvulsant screens and in genetic models of absence epilepsy and audiogenic seizures (Bialer et al., Epilepsy Res. 83:1-43; 2009). It powerfully decreases chronic spontaneous motor seizures after kainate-induced status epilepticus (SE); and its antiepileptogenic activity was inferred in the pilocarpine-induced SE model. We assessed the antiepileptogenic and antiepileptic effects of CRS in a blind, randomized study using an etiologically realistic rodent model of posttraumatic epilepsy (PTE) that is resistant to carbamazepine and responsive to valproate in a subset of subjects (Eastman et al., Exp Neurol. 2010).

Methods: Rats (Sprague-Dawley males, pnd 31-6) were randomized to treatments after rostral parasaggital fluid percussion injury (FPI; 3.4 atm). Antiepileptogenic effects of CRS were assessed (48h video-ECoG/wk) in 22 control and 27 CRS-treated rats, 2 and 10 weeks after completion of a 2 week prophylactic treatment begun 15 min after injury. The antiepileptic effect of CRS was assessed in a repeated measures experiments at 4-5 weeks (n=8) and 16-17 weeks (n=7) post-injury (48-72h video-ECoG/wk). Rats received CRS 3 times daily for a week, on weeks 5 and 17 postinjury. Treatment was delivered orally in opaque condensed milk vehicle drawn from coded vessels. Dosing regimens were designed to provide stable plasma CRS, and levels were monitored in both studies. ECoG files were analyzed in random order by personnel held blind to their identity. Antiepileptic and antiepileptogenic studies were powered (0.8, á=0.05) to detect ~50% and ~80% uniform decreases, respectively.

Results: Prophylactic CRS treatment did not decrease seizure frequency at either time point. The mean frequency of seizure 4 weeks after FPI was 1.4±0.6 events/h in controls and 1.5±0.4 events/h in CRS rats. By 12 weeks post-FPI these had increased to 2.1±0.7 and 3.4±1.4 events/h in the control and CRS groups, respectively.

Antiepileptic CRS treatment did not decrease seizure frequency compared to corresponding pre-treatment intervals during CRS treatments administered on post-injury weeks 5 and 17. Week 4 seizure frequencies were 1.9±0.6 and 2.2±1.2 in the control and CRS groups respectively. In controls, the log-transformed frequency of seizure (LTF) was stable at 0.02±0.23 on week 4 and 0.04±0.28 on week 5. LTF in the treatment group was unaffected by CRS; it was -0.13±0.24 at week 4 and -0.13±0.26 at week 5 on drug, and 0.6±0.2 at week 16 vs 0.8±0.2 at week 17 on drug.

Conclusions: We detected no antiepileptogenic or antiepileptic effect of CRS on FPI-induced PTE despite $[CRS]_{plasma}$ at least comparable to levels attained in previous studies. These data further support FPI-induced PTE as a model of pharmacoresistant epilepsy.

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3.036

DIFFERENTIAL NEURONAL ACTIVATION PATTERN AND SEIZURE SUSCEPTIBILITY IN NEWBORN RAT PUPS FOLLOWING MATERNAL STRESS AND IMMUNE CHALLENGE

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Rationale: The underlying pathophysiology in the majority of pediatric epilepsies is still incompletely understood. To improve this understanding new models are needed that mimic the reality that most cases of pediatric epilepsy are non-lesional and unlikely to be from a single gene abnormality. Herein we describe the behavioral and anatomical features of a new model of seizure susceptibility.

Methods: Groups of three pregnant Sprague Dawley female rats were transported either during early (EG), or middle (MG), gestation and subsequently assigned to one of three groups: naïve, control (saline i.p.) or experimental (LPS; 100 µg/kg i.p.). Injections were performed on the 15th day of gestation (G15). Pregnancy and parturition then proceeded undisturbed and pups remained with their mothers. Pups were then challenged with a febrile convulsions (FC) paradigm on the 14th post natal day (P14) involving an injection of 200 µg/kg of LPS followed 2.5 hours later by 1.75 mg/kg of kainic acid and videotaped for 3 hours for behavioral scoring. Twenty-four hours after seizure provocation animals were euthanized and their brains processed for immunohistochemical reactivity (IR) and analysis of FosB, c-fos, c-jun, protein expression as well as Fluoro-jade C expression using standard procedures.

Results: The paradigm did not adversely affect parturition nor alter the typical litter size or sex ratio. Maternal transport during later gestation however resulted in increased pup seizure severity and more lethal events ($p<0.001$). Both prenatal saline and LPS at G15 decreased pup seizure severity in a graduated manner: an effect that was seen at both transport times ($p<0.05$ to $p<0.001$). Qualitative and quantitative immunohistochemical analysis revealed significant differences in FosB-IR expression in the hippocampal subregions, amygdala, piriform, entorhinal and retrosplenial cortices, nucleus accumbens, periventricular regions of both the thalamus and hypothalamus, the substantia nigra and the locus coeruleus ($p<0.05$ to $p<0.001$). Similar patterns were observed in the IR expression of c-fos and c-jun with slight variations. This differential expression did not appear to be a result of cell death as there was minimal expression of Fluoro-jade C.

Conclusions: These results suggest that maternal prenatal stress and immune challenge modify newborn seizure susceptibility and that the

magnitude and direction of the effect was dependent on the timing of the stressor(s). Further, the combination of the FC-induced behavioral manifestations and neuronal activation pattern in the P14 pups suggests a change in the circuit activation that was related to the maternal prenatal stress. Ongoing studies are examining both the underlying pathophysiological mechanisms of the model, as well as the impact of the prenatal stressors on neurodevelopment and epileptogenesis.

3.037

CONFIRMATION OF MULTIPLE SEIZURE SUSCEPTIBILITY QTLS ON CHROMOSOME 15 IN C57BL/6J AND DBA/2J INBRED MICE

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Rationale: Due to their extreme differences in response to many types of seizure-evoking stimuli, C57BL/6J (B6) and DBA/2J (D2) mice represent a genetic model with relevance to epilepsy. To confirm seizure susceptibility (SZS) QTLs on chromosome (chr) 15 that were identified previously using B6 and D2 mice, and to refine their genomic map position, we studied a set of three congenic strains in which overlapping segments of chr 15 from D2 were transferred onto the B6 background.

Methods: We measured thresholds for generalized electroshock seizure (GEST) and maximal electroshock seizure (MEST) in congenic strains and B6-like littermates and also tested their responses to systemic injection of kainic acid (KA) and pentylenetetrazol (PTZ).

Results: Results document that MEST is significantly lower in strains 15M and 15D, which harbor medial and distal (telomeric) segments of chr 15 (respectively) from D2, compared to strain 15P, which harbors the proximal (acromeric) segment of chr 15 from D2, and to control littermates. Congenic strains 15P and 15M exhibited greater KA SZS compared to strain 15D and B6-like controls. All congenic strains were similar to controls with regard to PTZ SZS.

Conclusions: Taken together, results suggest there are multiple SZS QTLs on chr 15 and that two QTLs contain gene variants that affect MEST and KA SZS independently. The MEST QTL is refined to a 19 Mb region flanked by rs13482630 and D15Mit159. This interval contains 350 genes, 183 of which reside in areas that are not "identical by descent" between B6 and D2 and where the polymorphism rate is high. The KA QTL interval spans a 65 Mb region flanked by markers D15Mit13 and rs31271969. It harbors 83 genes in highly polymorphic areas; 310 genes in all. Complete dissection of these loci will lead to identification of genetic variants that influence SZS in mice and provide a better understanding of seizure biology.

3.038

ANTIEPILEPTIC DRUGS (AEDS) IN NEONATAL RATS DISRUPT STRIATAL SYNAPTIC MATURATION

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Rationale: The striatum is especially vulnerable to pro-apoptotic effects of certain AEDs given to neonatal rats. We asked if this toxicity alters the maturation of GABA and glutamate transmission in striatum. We examined synaptic currents in medium spiny neurons (MSNs, striatal output neurons), from postnatal day (P)10 to 18 in rats exposed on P7 to one treatment of phenobarbital (PB), phenytoin (PHT), lamotrigine (LTG), or levetiracetam (LEV). To assess long-term outcomes, separate groups were evaluated for locomotor activity and reversal learning as juveniles (P21), and for water maze navigation as adults.

Methods: Inhibitory and excitatory post-synaptic currents (I and EPSCs) were recorded from MSNs on P10, P14 and P18 using whole cell voltage clamp in corticostriatal slices. P7 pups received: saline, PB (37.5 or 75mg/kg), PHT (50mg/kg), LTG (20mg/kg), or LEV (200mg/kg). Another group received melatonin (MEL 20 mg/kg) pretreatment before PB (75mg/kg) on P7 to determine if MEL, a compound effective for preventing PB-induced cell death, could attenuate the effects of PB. For behavioral testing in juveniles, P7 pups received PB (75mg/kg) or saline, and were tested on P21 on reversal learning in a T-maze, and locomotor activity in the with and without amphetamine (AMPH 1.5mg/kg). For behavioral testing in adults, pups were exposed daily from P7-14 with PB (75mg/kg) or saline and tested at 12 months in a standard water maze (hidden platform) task.

Results: In controls, m and sIPSC frequency increased 2x from P10 to 14 and an additional 50% by P18. IPSC amplitude and decay decreased from P10 to 18. EPSC frequency increased from P14 to 18 with no change in amplitude. P7 exposure to PB or PHT abolished the increase in IPSC and EPSC frequency from P10 to 18. LTG exposure at P7 resulted in similar but transient deficits. LEV was without effect. MEL pretreatment prevented the PB-induced disruption of IPSC frequency on P14. PB exposed pups showed normal t-maze acquisition but significant impairment in reversal learning at P21. They also showed greater locomotor activation than controls in response to AMPH. Adults exposed as pups to PB had longer escape latencies than controls during acquisition in the water maze and displayed excessive thigomotaxis; in a probe test (platform removed) they performed at chance levels.

Conclusions: Our data indicate that the normal developmental pattern of maturation of striatal GABAergic and glutamatergic synapses, as measured by age-dependent increases in IPSCs and EPSCs, is disrupted by P7 exposure to PB, PHT, or LTG, but not by exposure to LEV, a drug that does not cause cell death in neonatal rats even at high doses. Together with the ability of MEL to prevent the effect of PB, the results indicate that cell death may be a determinant of this disruption. The behavioral impairment seen in both juveniles and adults exposed to PB postnatally, may reflect long-term consequences of earlier disruption in synaptic maturation in striatum. These results underscore the need to identify and select antiepileptic treatments that avoid acute and long-term neurotoxicity in the developing brain.

3.039

EARLY LIFE STATUS EPILEPTICUS COMPROMISES NONASSOCIATIVE LEARNING AND INCREASES ANXIETY IN JUVENILE RATS

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Rationale: Present study was designed to characterize effects of early SE on development of cognitive abilities, adaptability and emotionality

in short intervals after insult. Animals were tested using open field paradigm around weaning period, puberty onset and as young adults.

Methods: SE was induced by pilocarpine (40 mg/kg) in LiCl (3meq/kg) pretreated P12 rats. To prevent mortality and to improve recovery rats were given a single dose of paraldehyde (0.3 mg/kg) 2h after SE onset. Controls received saline instead pilocarpine. The open field (OF) test was used to check the behavioral responses to novel environment, motor abilities, emotional stage and habituation. The animals were exposed to the OF box (45x45x30 cm) four times (6, 13, 26 and 40 days after SE) always for 5 minutes. Behavior was analyzed using EthoVision (Noldus Information Technology; The Netherland) and in addition to parameters of ambulation also time spent in central and peripheral zone, number of entries of central and peripheral zone and corners, incidence of wall leaning and rearing and duration of grooming were evaluated. Habituation, a non-associative learning process, was assessed as a progressive decrease of motor activity during the 5-min testing interval.

Results: SE developed in all 24 animals. Clinically, status epilepticus was characterized by twitching of facial muscles, chewing, head bobbing, forelimb clonus, tail erection and "swimming" movements. Paraldehyde in a single dose of 0.3 ml/kg suppressed motor seizures. Mortality during 24h after SE was 42%, no animals died later. Slight decrease of the body weight was seen 24h after SE (3% decrease whereas controls gained 17 % of their weight at P12). Behavior in the open field was changing with age at the exposure. Animals with SE did not start to habituate before the second test whereas in controls the first signs of habituation occurred already at P18. In test 1, 2 and 3 SE animals prefer to stay in periphery (i.e. safe area) and they also explored central zone (i.e. dangerous area) less frequently than controls. Incomplete grooming as well as freezing was more often seen in SE than in control rats. These data suggest higher anxiety and altered adaptation in animals with SE compared to their intact siblings. In contrast, there was no difference in velocity of ambulation between these two groups suggesting that observed changes are not due to SE-induced motor impairment.

Conclusions: SE during early postnatal development leads to developmental delay of cognitive abilities and to increase of emotionality later in the life. In contrast, motor abilities are not impaired.

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3.040

STROKE-RELATED HYPER EXCITABILITY IN A NOVEL ACUTE IN VITRO MODEL OF FOCAL ISCHEMIA

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Rationale: Post-stroke epilepsy represents 11 % of all epilepsy and 22%of all cases of status epilepticus (Camilo 2004; De Lorenzo 1996; Herman 2002). Animal models of stroke-induced epilepsy are potentially useful to study the temporal evolution of acquired epilepsy and to identify the molecular and cellular mechanism underlying epileptogenesis.

In the present study we investigate phenomena of hyperexcitability in a new in vitro model of focal ischemia in which the preservation of the tridimensional connections between close and remote brain areas are maintained. In particular we assessed if i) acute alterations induced by focal ischemia are associated with changes in synaptic excitability and ii) enhanced excitatory networks would lead to abnormal epileptiform activity.

Methods: Permanent focal ischemia was induced by the occlusion of either the anterior cerebral arteries (ACAs) or one of the rostral posterior cerebral arteries (rPCA) was performed in the isolated guinea pig brain maintained in vitro by arterial perfusion

Results: Simultaneous extracellular recordings performed with multiple electrodes positioned in brain areas within and outside the vascular territory of the occluded vessels revealed transient ischemic depolarizations (ID) exclusively in the core territories involved by the ischemic insult. The propagation and spatial distribution of IDs observed in the ischemic area strictly correlated to the ischemia-induced tissue damage successively defined by immuno-histochemical analysis with antibodies anti- mictotubule-associate protein (MAP-2) and by MRI analysis. In particular, TrD maps demonstrated areas of hypointensity that closely correlate to the MAP-2 negative areas (Pastori et al, 2007; 2008; Breschi et al, 2010). Phenomena of hyper excitability in the ischemic core and penumbra were analyzed by paired-pulse stimulation of the lateral olfactory tract at low and high frequency unmasked by comparing the amplitudes of mono-and di-synaptic responses between conditioning (first) and conditioned (second) paired stimuli.

Conclusions: At the light of these results we demonstrated that the in vitro isolated guinea pig brain preparation is suitable to study the correlation between anatomical/MR and electrophysiological changes and to evaluate early acute alterations in excitability occurring after an ischemic insult.

3.041

ANIMALS WITH MALFORMATIONS OF CORTICAL DEVELOPMENT HAVE RELATIVELY NORMAL EEG AND PLACE CELL CHARACTERISTICS

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Rationale: Malformations of cortical development (MCD) are a common cause of epilepsy and cognitive impairment. Rats injected with methylazoxymethanol (MAM) exhibit varying degrees of MCDs and impairments of spatial navigation when tested in the Morris Water Maze. It is known that in normal rodents spatial navigation is supported by place cell activity which is modulated by hippocampal EEG, particularly the "theta" rhythm. MAM administration during gestation affects the migration of parvalbumin interneurons; a cell type known to modulate EEG oscillations. Therefore we hypothesize that animals exposed to MAM during development will have abnormal oscillatory activity in the EEG which will affect place cell function.

Methods: Two pregnant Dams were injected with 20mg/kg MAM, a DNA methylating agent, either at embryonic day (E) 15 or 17 to vary the severity of MCDs. At P22-25 rats (n=2) from each litter were implanted with custom microdrives with electrodes aimed at the dorsal hippocampus. After surgery, electrodes were lowered by steps of 20im every 4 hours until single unit activity was detected. Hippocampal pyramidal cell activity was then recorded each day for two 12min sessions, separated by a 15min interval.

Results: Hippocampal EEG spectral analysis of MAM rats (n=2) exhibits identifiable theta and gamma rhythms in the EEG. As in controls, gamma power was modulated by theta power. In the MAM E15 animal 18 cells were recorded; 2 were interneurons and 13 were characterized as place cells. The firing rate of 9 of the place cells was theta modulated. Only 2 place cells were stable between the two sessions. In the MAM E17 animal 14 cells were recorded, including one interneuron. Amongst the 7 identified place cells, 5 were theta modulated and 3 were stable between sessions.

Conclusions: Our preliminary data show that the networks subserving spatial navigation are present in animals with extensive MCDs. It is now important to establish whether these networks function normally by comparing animals with MCDs to control animals. Abnormal network function may be an important contributor to cognitive impairment observed in these animals. Thus, modification of network function may represent a novel therapeutic target for improving cognitive outcomes in patients with epilepsy and MCDs.

3.042

HIGH DOSE PHENOBARBITAL DECREASED SEIZURE SUPPRESSION AND LOST NEUROPROTECTION, COMPARED TO LOW DOSE, IN IMMATURE MOUSE MODEL OF STROKE

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Rationale: Stroke in neonates and infants presents with seizures that are frequently treated with phenobarbital. We hypothesized that anticonvulsants attenuate ischemic injury, however, age- and injury-dependant differences in gene expression determine the brain's response to GABA enhancement.

Methods: P12 CD1 mice received common carotid ligation, and immediate phenobarbital (30 mg/kg or 60 mg/kg i.p.) or vehicle, and acute seizures were scored. 5 doses of BrdU (50 mg/kg/dose) were administered i.p. between P18-P20, cognitive testing done between P32-P37, and mice were perfused at P40. Brain atrophy was quantified, and DG BrdU-labeled cells counted. Mice injected with 30 mg/kg or 60 mg/kg phenobarbital or vehicle i.p. had respiratory rates observed 2 hours later and blood levels measured 4, 12, 24 or 36 hours.

Results: 33.3% (8/24) of injured mice receiving 30 mg/kg phenobarbital seized (median seizure score=0, range 0-20, $p<0.01$ versus vehicle), 70% (14/20) of injured mice receiving 60 mg/kg phenobarbital (median seizure score=7.5, range 0-15, $p=0.034$ versus vehicle) and 63.6% (14/22) of injured mice given vehicle (median seizure score=16, range 0-75) displayed seizures. Hippocampal and hemispheric atrophy in 30 mg/kg treated injured mice were 47.3% and 20.3% (N.S. and $p<0.01$ versus vehicle), 67.2% and 46.7% in 60 mg/kg treated (both p=N.S. versus vehicle), and 60.2% and 42.9% in vehicle-treated injured mice. Counts of rears during open-field testing in mice receiving 60 mg/kg of phenobarbital were significantly less than the other two groups and less than uninjured animals. Additionally, vehicle and 60 mg/kg PB-treated injured animals both spent significantly less time rearing than their uninjured counterparts. Between session habituation was impaired in the vehicle and 60 mg/kg treated injured groups, while 30 mg/kg restored habituation in injured animals. The percent decrease in BrdU+ counts (ipsilateral to contralateral) showed a trend for a greater decrease in the 60 mg/kg group. The 60 mg/kg dose eliminated the significant correlations between seizures and hippocampal injury. Peak blood levels were 25.4±2.0 mg/dl (n=2) at 4 hrs after 30 mg/kg and 46.9±1.6 mg/dl (n=2) after 60 mg/kg. Respiratory rates were not significantly different between groups.

Conclusions: Doses achieved clinically relevant plasma concentrations. 30 mg/kg phenobarbital administered immediately after stroke reduced acute seizures and chronic hemispheric brain injury and restored habituation and exploratory behavior. 60 mg/kg, by comparison, was a less efficacious acute anticonvulsant, was not neuroprotective, and impaired behavioral and cognitive recovery. The lack of correlation between seizures and injury in the 60 mg/kg animals suggests that this dose produces toxicity by some mechanism rather than simple loss of neuroprotective effect. No evidence of respiratory rate depression was noted and current work is addressing other possible mechanisms of this phenobarbital dose effect.

3.043

SPONTANEOUS CONVULSIVE SEIZURES AND SPIKE-WAVE DISCHARGES IN AGED ALZHEIMER'S DISEASE MICE

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Rationale: Alzheimer's disease (AD) is associated with a significantly increased risk of seizures. Approximately 7-21% of patients with AD will have at least 1 seizure during the duration of their illness, and the incidence may be as high as 80% in certain familial cases. Recent evidence suggests that neuronal hyperexcitability may contribute to the memory impairments in AD. Transgenic AD mice, harboring a mutated human amyloid precursor protein, were reported to have frequent seizures and epileptiform activity. These animals were further shown to have compensatory inhibitory sprouting in the dentate gyrus of the hippocampus, which could have a significant adverse effect on memory function. Despite these important findings, seizures in animal models of AD have not been fully characterized. Specifically, age-dependent impairments in spatial memory seen in AD mice may not be detectable until 12 months of age, and the severity of seizures at this age is not known. In this study we characterize seizures and epileptiform activity in aged double transgenic AD mice by continuous in vivo video-EEG monitoring. Characterizing EEG abnormalities in both animal models and AD patients is a critical step towards assessing antiepileptic therapy as part of a comprehensive treatment strategy for patients with AD.

Methods: 10 double transgenic AD mice (APPswe/PSENÄE9) and WT controls (C57B6) underwent EEG electrode implantation and 3-channel continuous video-EEG monitoring (Pinnacle Systems). The mice were anesthetized, and 6 screw electrodes drilled into the skull. The electrode contacts were attached to a 6-pin connector, and secured using dental acrylic. Each animal underwent a total of at least 48 hours of continuous EEG recordings at ages 8 and 12 months. EEGs were analyzed manually, with the examiner blinded to genotype.

Results: The majority of transgenic AD mice showed significant spontaneous EEG abnormalities compared to WT controls. These included multiple convulsive seizures, isolated epileptiform discharges, and brief spike-wave seizures (SWS) with full behavioral arrest. Spike-wave seizures have not previously been described in AD mice.

Conclusions: Our results demonstrate that seizures are common in aged double transgenic AD mice. The finding of spike-wave seizures in this mouse model is of particular interest as they could clearly affect cognitive performance, and would be impossible to detect without video-EEG monitoring. Future investigations will be important to elucidate the mechanisms underlying seizures in AD. We have previously shown that cellular prion protein (PrPC) is required for memory impairments and other prominent phenotypes in double transgenic AD mice, and we are now assessing the role of PrPC in mediating the aberrant neuronal hyperexcitability demonstrated in our crrent study. Our data presented here would support prospective long-term EEG monitoring of patients with AD to fully characterize the incidence of seizures in this patient group. This could lead to future studies evaluating the use of effective anticonvulsant therapy as a novel treatment strategy in AD.

IMAGE: images/905395_A.jpg

Figure 1. Spontaneous seizures and epileptiform discharges in a double transgenic Alzheimer mouse model. A typical tonic-clonic seizure lasting approximately 1 minute (A). Spike-wave seizure associated with brief behavioral arrest (B). These seizures have not previously been characterized in AD mice. A typical epileptiform discharge observed in the transgenic mice (C). All animals were 8-12 months of age.

3.044

MODIFICATION OF STATUS EPILEPTICUS MODELS TO SIMULATE TEMPORAL LOBE EPILEPSY WITHOUT EXTENSIVE BRAIN DAMAGE

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Rationale: Rodent models of temporal lobe epilepsy (TLE) typically initiate epileptogenesis using a convulsant or electrical stimulation to induce status epilepticus (SE). Ultimately the animals develop lifelong seizures, so these models have been extremely valuable to ask questions about epilepsy. However, they have been criticized because widespread neuronal loss typically follows SE, and it has been pointed out that the extensive damage does not characterize TLE well. We hypothesized that decreasing neuronal damage would lead to a model that offered new opportunities to investigate TLE. Therefore, we modified the methods that are commonly used in SE models and evaluated the outcome.

Methods: Adult male and female Sprague-Dawley rats (2-3 months old) were treated with pilocarpine or kainic acid (i.p. or s.c.) to elicit status epilepticus (SE), and after 1 hr they were treated with pentobarbital (10 mg/kg, i.p.). Comparisons were made to animals treated with pentobarbital at other times (5-60 min) or diazepam (10 mg/kg, i.p.). Three days after SE, animals were perfused with 4% paraformaldehyde and sectioned to evaluate neuronal death using fluorojade-B histochemistry. In other animals, EEG (2-6 months after SE; Bio-Signal Group) was conducted using 2 dorsal hippocampal electrodes and 4 epidural cortical electrodes. After these animals were perfused (>2 months after SE), antibodies to neuronal and glial markers were used (NeuN, GFAP, calbindin D28K, neuropeptide Y) to quantify pathology (Image J; StereoInvestigator) using a brightfield microscope (Olympus BX51).

Results: Animals that were treated with kainic acid (12 mg/kg, s.c.) and pentobarbital (10 mg/kg, i.p.) after 1 hr of SE provided the most reproducible approach, with all animals exhibiting SE (100%; 23/23), no mortality, and decreased morbidity with respect to food intake in the days after SE. Female reproductive function persisted as indicated by regular estrous cycles. Interestingly, spontaneous stage 5 convulsions were rare after SE (<1/week by 24 hr video recording 3 months after SE; n=4). However, stress (induced by restraint) initiated stage 5 convulsions readily. EEG recordings revealed non-convulsive seizures and interictal spikes that increased in frequency over the first 6 months after SE. Anatomical evaluation demonstrated limited neuronal damage, with preserved hippocampus, neocortex, and minimal enlargement of the ventricles. Neuronal loss primarily occurred in entorhinal cortex, amygdala, and piriform cortex.

Conclusions: The relative preservation of the brain and ease of use of the modified model, relative to previous methods where SE is more severe, provides opportunities to evaluate aspects of TLE such as progression and the effects of stress, variables that are important clinically. This model also preserves reproductive function, allowing opportunities to investigate the relationship between reproductive hormones and TLE. Finally, an animal model of TLE with primarily extrahippocampal pathology provides a complement to pre-existing models where the hippocampus exhibits extensive neuronal loss.

3.045

LOW BLOOD GLUCOSE INCREASES ABSENCE SEIZURE SUSCEPTIBILITY

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Rationale: Absence epilepsies are a common disease with a strong genetic aetiology. Certain environmental factors can influence absence occurrence but a complete understanding of absence precipitation is lacking. Here we investigate if lowering blood glucose increases spike-wave activity in mouse models with varying seizure susceptibility.

Methods: Three mouse models were used; an absence seizure model based on the knock-in of a human GABAAã2(R43Q) mutation (DBA(R43Q)), the spike-wave discharge (SWD)-prone DBA/2J strain, and the seizure resistant C57Bl/6 strain. Electrocorticogram recordings were made to measure SWDs from mice prior to and following injection of various doses of insulin. Blood glucose was independently measured to determine the reduction in levels following insulin injection.

Results: A ~45% reduction in blood glucose levels (6.7±0.3 mM to 4.0±0.4 mM, n=10, $p<0.05$) was sufficient to double SWD occurrence in the DBA(R43Q) model (19.9±5.9 to 50.3±5.9 SWD/h, n=10, $p=0.001$) and in the SWD-prone DBA/2J mouse strain(1.1±0.5 to 1.8±0.4 SWD/h, n=7, $p=0.01$). Larger reductions in blood glucose further increased SWDs in both these models. However, even with large reductions in blood glucose no discharges were observed in the seizure-resistant C57Bl/6 mouse strain (n=6). Injection of glucose reversed the impact of insulin on SWDs in the DBA(R43Q) model (48.5±14.2 to 20.5±9.8 SWD/h, n=5, $p=0.02$), supporting a reduction in blood glucose as the modulating influence.

Conclusions: Low blood glucose can reduce seizure threshold in genetically predisposed animal models and should be considered as a potential environmental risk factor in absence epilepsy patients.

3.046

ACUTE Aâ NEUROTOXICITY INDUCES HIPPOCAMPAL SCLEROSIS WITH SEIZURES INDEPENDENT OF ALZHEIMER'S PATHOLOGY

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Rationale: Epileptic seizures constitute a frequent comorbidity of Alzheimer's disease; however, the pathophysiology of seizure-generation in Alzheimer's disease remains poorly defined. A common pathological hallmark of both Alzheimer's disease and epilepsy is astrogliosis— a cellular process that causes overexpression of adenosine kinase leading to adenosine deficiency and seizures. We hypothesize that astrogliosis and a resulting deficiency of the brain's endogenous neuroprotectant and anticonvulsant adenosine might be the causative agent of seizures in Alzheimer's disease. Here, we developed and characterized a novel mouse model of acute amyloid-beta (Aâ) induced epileptogenesis that is based on a single high dose injection of $Aâ_{1-40}$ into the dentate gyrus of wild-type mice.

Methods: Aggregated human $Aâ_{1-40}$ (200 pmol / 1.5 ìl) or saline (negative control) was unilaterally microinjected in the dentate gyrus of adult C57BL/6 male mice. Acute injury to the hippocampus was assessed 24 hours later by Nissl and TUNEL stains in $Aâ_{1-40}$ and saline controls (N = 5, each). The chronic affects of $Aâ_{1-40}$ or saline (N = 6, each) were assessed 4 weeks after microinjection by (i) unilateral bipolar EEG recordings in the CA1 subregion and (ii) detailed histological analysis. To define the role of adenosine in $Aâ_{1-40}$-related seizures the adenosine kinase inhibitor ITU (3.1 mg / kp, i.p.) and the adenosine A1 receptor agonist CCPA (3.0 mg / kg, i.p.) were administered during EEG recordings.

Results: $Aâ_{1-40}$ caused acute neurotoxicity with extensive neuronal apoptosis in the dentate gyrus (247 $\pm$ 65 TUNEL positive cells / section) and CA1 (113 $\pm$ 33 TUNEL positive cells / section) that was absent in saline injected controls. Four weeks after $Aâ_{1-40}$ injection, all animals displayed prominent hippocampal atrophy (46 % loss of hippocampal volume vs. contralateral side, $p < 0.0001$) and astrogliosis within the dentate gyrus. Astrogliosis was associated with a 35 % increase in adenosine kinase compared to saline injected controls ($p < 0.001$). In line with the role of adenosine kinase as a regulator of hippocampal excitability, all animals experienced recurrent electrographic seizures (5.5 $\pm$ 0.32 seizures / h) that were recorded from intrahippocampal electrodes. Pharmacologically, seizures could be suppressed by ITU, an adenosine kinase inhibitor (0 seizures / h; efficacy period 3 h) or CCPA, an adenosine A1 receptor agonist (0 seizures / h; efficacy period 16 h), indicating that seizures were related to focal adenosine deficiency. Finally, $Aâ_{1-40}$ mediated hippocampal sclerosis and seizures occurs independent of Aâ plaque deposition, synthesis of endogenous $Aâ_{1-40}$, or cleavage of amyloid precursor protein into C-terminal fragments.

Conclusions: Our data indicate that (i) Aâ induced neurotoxicity can lead to the development of spontaneous seizures via a gliosis- and adenosine-related mechanism and (ii) that electrographic seizures, related to gliosis, as is commonly observed in Alzheimer's disease, might occur prior to the onset of "classic" Alzheimer's pathology.

3.047

ESTIMATING STATE-OF-VIGILANCE DYNAMICS TO IMPROVE PREDICTION OF EPILEPTIC SEIZURES

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Rationale: Ample clinical and experimental evidence indicates that there is a link between seizure and sleep dynamics (Dinner 2002). There is now a focused effort in the development and clinical implementation of neural prosthetics for the prediction and control of epilepsy. However, seizure prediction efforts have largely ignored the known and confounding effect of state-of-vigilance (SOV) on seizure states; likely due to the difficulty of classifying SOV using measurements obtained from implanted devices. Our aim is to develop an observer/predictor system, suitable for implantable devices that will track and predict sleep-wake cycles as well as the underlying dynamics to improve seizure prediction.

Methods: We have implemented a chronic, behaving animal model of limbic epilepsy in the free-moving rodent. We continuously record and monitor depth and cortical EEG as well as movement information obtained from head-mounted accelerometers which, in the past, we've demonstrated can be used for accurate SOV classification. We have now implemented biologically-based models of sleep dynamics that embody the cellular networks involved, and have applied nonlinear data assimilation methods (Schiff 2010) to use these models as observers and predictors of state of vigilance.

Results: Here we demonstrate that this methodology works well in the case of assimilation of observations from one computational model into an observer model based off the same or different model (Diniz Behn 2007, Tamakawa 2006). We also present results from assimilation of rodent data into one of the models. This assimilation allows us to reconstruct the physiological model using data obtained from our experimental rodents. Thus, we gain access to previously 'hidden' variables that describe sleep dynamics. Finally, we demonstrate that we can use the existing algorithm to make short-term predictions of sleep state and sleep state transitions.

Conclusions: It is becoming increasingly clear that in order to predict and control seizure dynamics, we must first be able to grasp the dynamics of sleep and sleep-state transitions. Although several biologically inspired models of sleep have been recently published, their implementation has been limited to computer simulations. Using our data assimilation approach, we are able to combine the advances in computational modeling of sleep together with measurements from our experimental rodents, to access the dynamics of the underlying network which govern both sleep and seizure state transitions. Thus, our work bridges experimental and computational techniques to investigate a crucial 'missing link' which will give us insight into the dynamics of seizures and may drastically improve seizure prediction.

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3.048

BRD2 HAPLOINSUFFICIENCY PREDISPOSES FOR GABA DOWNREGULATION, INCREASED SEIZURE SUSCEPTIBILITY, AND SPONTANTEOUS SEIZURES

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Rationale: In humans, the linkage and association of BRD2 gene to juvenile myoclonic epilepsy (JME) has been replicated by multiple studies. In mice, the Brd2 null mutation (Brd2-/-) is embryonic lethal at mid-gestation and the embryos exhibit abnormal neural development. The heterozygous Brd2+/- mice are viable, enabling us to study both seizure susceptibility and look for anatomical changes in underlying brain structures that, in comparison with +/+ controls, could explain an effect on seizures. The anatomical changes were investigated in the structures involved in control of generalized seizures, i.e., in the basal ganglia network.

Methods: The Brd2 knock out mice were created using a gene-trap approach (Shang et al, Dev Dyn 238:908-17; 2009). Seizure susceptibility was tested using flurothyl. Spontaneous seizures were recorded with EEG/videomonitoring setup with infrared capability. GABAergic markers (parvalbumin and GAD67) were detected using immunostaining. Relative numbers of immunopositive cells were compared between +/- and +/+ mice and densitometry was used to compare immunoexpression of staining in the primary motor cortex, striatum/globus pallidus, the substantia nigra, and the superior colicullus.

Results: Seizure susceptibility was changed in sex-specific fashion: Male Brd2+/- had decreased threshold for clonic seizures, while female Brd2+/- mice for tonic-clonic seizures compared to +/+ mice of the respective sex. We performed long-term EEG/videorecordings in five Brd2+/- mice. In the three mice (out of five observed to date), spontaneous clonic seizures were recorded ranging in duration from several seconds to tens of minutes. One mouse died while in status epilepticus. Immunohistochemistry and cell number comparisons demonstrated significant downregulation of GABA markers irrespective of sex in the primary motor cortex, substantia nigra reticulata, and superior collicullus, but not in the hippocampus in Brd2+/- mice in comparison with +/+ controls.

Conclusions: Our study is the first to demonstrate a non-channel JME gene associated with downregulation of GABA markers, increases in seizure susceptibility and occurrence of spontaneous seizures. These findings strengthen the hypothesis that mutations in human BRD2 gene contribute to the occurrence of JME. The impairment of the GABAergic system suggests that a mechanism for IGE may be a deficit of GABAergic neurons.

3.049

A POTENTIAL TREATMENT FOR INFANTILE SPASMS: AN EVIDENCE FROM THE ANIMAL MODEL OF CRYPTOGENIC INFANTILE SPASMS

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Rationale: Infantile spasms are refractory to conventional antiepileptic drugs, while ACTH is a drug of choice. We developed a model of the cryptogenic infantile spasms, characterized by the spasms responding to ACTH (Ann Neurol 2007 (61)109-119). Recently we showed that melanocortin 4 receptors (MC4R) are responsible for the effect of ACTH against the spasms in our model (Epilepsia 2009 (50) Suppl. 11, 375). Here we examined other MC4R agonists against the spasms using our model.

Methods: We used the offspring from mothers injected with betamethasone on G15. Prenatally betamethasone exposed rats were implanted with a guide cannula to the lateral ventricle on postnatal day (P)13. On P15, pups were pretreated with i.c.v. administered MC4R agonists; alpha-MSH (1nmol), THIQ (1nmol), or Ro273225 (6.5 nmol). Controls received 0.5µL saline (vehicle) i.c.v.. Additional prenatally betamethasone exposed rats were treated using systemic administration (i.p.) of THIQ (1mg/kg) or Ro273225 (100 µg/kg). After 60min following any drug treatment, NMDA was administered intraperitoneally to trigger the spasms and the latency to onset of flexion spasms and the number of spasms were evaluated.

Results: Intraventricular administration of THIQ, Ro273225 and alpha-MSH significantly delayed the onset of NMDA induced spasms ($p < 0.05$) when compared to the saline-infused controls. On the other hand, systemic administration of THIQ or Ro 273225 had no specific effects on the latency to onset of spasms or the number of spasms ($p > 0.05$).

Conclusions: Despite of the lack of efficacy after the systemic administration, non-peptide MC4 receptor agonists and alpha-MSH significantly delayed the onset of spasms after i.c.v. administration. This suggests that the MC4 receptors play a significant role in regulation/modulation of cryptogenic infantile spasms in our model.

3.050

EEG CORRELATES OF CATAMENIAL EPILEPSY IN INTACT FEMALE RATS

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Rationale: In women with catamenial epilepsy, seizures worsen at certain times of each menstrual cycle. Reports concerning the prevalence of this syndrome vary. It is possible that catamenial patterns are underestimated because the EEG exhibits patterns more than convulsive behaviors. We tested this hypothesis using EEG recording of intact epileptic female rats. We chose an animal model of temporal lobe epilepsy (TLE), because patients with foci in the

temporal lobe appear to be more susceptible to catamenial patterns (Herzog, 1999; Quigg et al., 2009).

Methods: Adult male and female Sprague-Dawley rats (2-3 months old) were treated with pilocarpine or kainic acid to elicit status epilepticus (SE), and after 1 hr they were treated with pentobarbital (10-20 mg/kg, i.p.). The selective estrogen-response modulator raloxifene (1-2 mg/kg, s.c.) was injected before pilocarpine. To record EEG, rats were implanted with 2 twisted bipolar electrodes in the dorsal hippocampus bilaterally and 4 epidural screws over the frontal and occipital cortices bilaterally. After 1-2 weeks, rats were recorded daily between 9:00 and 12:00 a.m. to collect up to 30 min of EEG during spontaneous periods of exploration, immobility, and sleep. Wideband signals (1-6000 Hz) were amplified 350x and transmitted by a digital telemetry device (Bio-Signal Group). The signal was amplified 2x, and sampled at 2 kHz/channel. The EEG was quantified using Insight (Persyst), custom-written macros in Igor (Wavemetrics), and Matlab (Mathworks). The regularity of the the estrous cycle was evaluated daily by vaginal cytology.

Results: Generalized interictal spiking (IIS), which occurred primarily during immobility and sleep, waxed and waned with the stage of the estrous cycle, with the most robust increase on estrous morning (n=4). All animals that became acyclic (n=10) or were ovariectomized (n=4) lost the cyclic increase in IIS frequency. In males, IIS frequency did not exhibit a cyclic pattern (n=2). Spontaneous stage 3-5 seizures were not exhibited when animals were evaluated with continuous video monitoring for 2 weeks (n=4), suggesting that intermittent convulsive seizures did not influence IIS frequency. However, the EEG often displayed 1-10s periods of continuous epileptiform activity accompanied by freezing behavior, suggesting non-convulsive seizures. In addition, stage 5 (convulsive) seizures were often triggered by handling when it involved restraint. Notably, these EEG findings appeared to be similar in rats treated with either pilocarpine or kainic acid.

Conclusions: SE in the intact female rat can lead to a cyclic increase in IIS frequency. The pattern that is exhibited appears to simulate the perimenstrual pattern of seizure exacerbation in catamenial epilepsy. Cyclic changes in IIS frequency were not detected in animals without regular estrous cycles, ovariectomized females, or males. The data suggest that catamenial epilepsy may be underestimated if convulsions are the only analysis of seizures.

3.051

INTRAPULMONARY MIDAZOLAM PROTECTS AGAINST CHEMOCONVULSANT SEIZURES IN MICE

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Rationale: The intranasal transmucosal route provides a convenient mode of midazolam delivery. Indeed, intranasal midazolam has been studied for over a decade as a pediatric sedative and for treating acute seizure clusters and status epilepticus. However, we considered whether the administration of midazolam directly into the lungs could provide better absorption and more direct delivery to the brain. The lung is highly vascularized and the thin alveolar epithelium represents a large absorptive surface that presents a minimal barrier to drug absorption. The intrapulmonary route therefore offers more rapid systemic delivery than does intranasal dosing and avoids first pass metabolism in the liver.

Methods: Midazolam was administered to mice via a tracheal cannula and by conventional intraperitoneal (i.p.) injection. The convulsant pentylenetetrazol (PTZ) was administered i.p (80 mg/kg). PTZ and a second chemoconvulsant kainic acid were administered intravenously (i.v.) at increasing doses to evaluate midazolam effects on seizure threshold.

Results: Midazolam (100 mg/kg, i.p.) induced loss of righting reflex within 8 min. Midazolam at much lower doses (100-1000 mcg/kg, i.p.) protected mice against clonic and tonic seizures and death induced by i.p. PTZ. Intratracheal midazolam was markedly more potent and more rapidly acting than with i.p. administration, providing protection against seizures and death at doses of 25-200 mcg/kg. Intratracheal midazolam at low doses also elevated the seizure threshold for i.v. PTZ and kainic acid. Intratracheal administration of cresyl violet dye revealed uniform distribution of the solution throughout the lungs.

Conclusions: Intratracheal midazolam provides potent and rapid seizure protection, indicating that intrapulmonary midazolam enters the alveoi and is rapidly absorbed into the blood stream and delivered to the brain. Midazolam administered by inhalation could be used to treat seizures. The pulmonary route of administration may offer advantages over intranasal delivery.

3.052

GENETIC AND BEHAVIOURAL CHARACTERIZATION OF A RODENT MODEL OF DEPRESSION AND EPILEPSY CO-MORBIDITY

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Rationale: The bi-directional co-morbidity between epilepsy and depression is likely due to similarities in neurobiological pathways and/or genetic influences, and is linked with decreased success of treatment. A valid animal model is essential for identifying the underlying mechanisms and developing novel therapeutics for this co-morbidity. Swim Lo-Active (SwLo) rats are a selectively-bred model for depression-susceptibility based on their phenotype on the forced swim test. We hypothesized that if the same genes govern both depression-susceptibility and seizure susceptibility, then SwLo rats should also be more susceptible to seizures. Previous research indicated that SwLo rats have increased mortality following kainic acid-induced seizures, suggestive of increased sensitivity. This study seeks to further validate the SwLo rats as a model of co-morbid epilepsy and depression and characterize the genes involved in the co-morbidity.

Methods: Swim Lo-Active (SwLo) and Swim Hi-Active (SwHi) rats were selectively bred for decreased and increased struggling in the forced swim test (FST) to create models of depression-susceptibility and resiliance, respectively. To assess seizure susceptibility, 380 mg/kg pilocarpine was administered i.p. and latency to motor seizure was measured. A second group of rats was assessed for electroshock-induced seizures using an increasing current electroshock (ICES) paradigm, allowing for determination of seizure threshold in individual rats. To identify candidate genes that may underlie this co-morbidity, we subjected hippocampal samples from five additional SwLo and SwHi rats to expression microarray analysis.

Results: We found that SwLo rats had higher sensitivity to pilocarpine- and electroshock-induced seizures compared with SwHi rats, validating these animals as a model of epilepsy and depression co-morbidity. Following administration of pilocarpine, SwLo rats showed

a significant decrease in latency to motor seizure compared to SwHi rats (19.73 min vs 55.09 min, t(20)=3.528, p=0.0021). Using the ICES paradigm, we determined that SwLo rats are indeed more susceptible to electrically-induced seizures than SwHi rats, as shown by a comparison of the threshold stimulation required to induce tonic flexion (13.83 mA vs. 17.33 mA, t(10)=9.391, p<0.0001).

Additionally, we found 210 genes that exhibited significantly different expression between the rat lines (fold change >2). Of these 210 genes, 121 had higher expression in the SwHi rats than the SwLo, while 89 genes showed higher expression in SwLo rats. Of particular interest were the genes Gabbr1, Gabrb2, and COMT (SwHi > SwLo), Hcn1 and Kcnj10 (SwLo > SwHi), which will be further characterized by RT-PCR and Western blotting.

Conclusions: These studies demonstrate the utility of SwLo rats as a model of co-morbid epilepsy and depression and provide potential candidates for novel therapeutics.

3.053

FAST RIPPLES IN AN EXPERIMENTAL NON-LESIONAL TEMPORAL LOBE EPILEPSY

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Rationale: Very fast ECoG activity, especially >250 Hz ("fast ripples"), has been implicated in epileptogenesis and seizure generation. Previous reports have concentrated on temporal lobe epilepsy with hippocampal sclerosis in both chronic experimental models and clinical cases. Here we determine whether fast ripples also provide a marker for the epileptic focus in an experimental temporal lobe epilepsy with no detectable neuronal loss.

Methods: We induced epileptic foci in anaesthetised rats by unilateral intrahippocampal injection of tetanus toxin, and implanted electrodes into ipsi- and contralateral CA3 and either CA1 or dentate gyrus. Recordings started 3-6 days after the operation, with sessions of a few hours repeated up to 21 days. At the end of the recordings the rats were killed by anaesthetic overdose and their brains were prepared for histology.

Results: A total of 60 electrographic seizures were recorded from 10 rats. The interictal periods were characterised by interictal discharges, typically lasting under 100 ms, and repeated epileptic discharges or polyspikes lasting a few seconds. 73% of seizures were first detected by the electrodes in the injected hippocampus, while interictal discharges could occur in either hippocampus alone or in both within a few ms. High-frequency activity was superimposed on both interictal and ictal activity and was analysed in both the frequency and time domains. The first spectral moment and the ratio between the powers of ripples (100-250 Hz) and fast ripples (251-600 Hz) both were higher in the injected hippocampus. These differences could be attributed to the more frequent occurrence of fast ripples in the injected hippocampus, and the similar rates of occurrence of ripples in the two hippocampi. Similar differences in high-frequency activity were recorded between the two sides during seizures.

None of the 7 rats that were analysed histologically showed evidence of neuronal loss.

Conclusions: Fast ripples can occur in epileptic foci lacking any discernible neuronal loss, and certainly without hippocampal sclerosis. In the tetanus toxin model fast ripples were always more common in the injected hippocampus, unlike interictal discharges and ripples, both of which were equally likely to occur in either hippocampus. We conclude that fast ripples are a more reliable marker for the primary epileptogenic zone than other kinds of interictal activity. Fast ripples should be considered for their potential contribution to pre-surgical work-up of non-lesional temporal lobe epilepsy.

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3.054

LONG-DURATION EPILEPTIFORM ACTIVITY IN MOUSE NEOCORTICAL SLICES ASSOCIATED WITH ZERO MG^{2+} / HIGH K^+ CONDITIONS: AN *IN VITRO* SEIZURE MODEL

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Rationale: The high potassium - low magnesium model is a relatively well established *in vitro* rodent model of ictogenesis for hippocampal epilepsy. However, data pertaining to its utility as a model of ictogenesis in neocortical epilepsies are sparse. In addition, little is known about the cellular and molecular mechanisms underlying the various types of rhythmic activities and their propagation in the cortex. The purpose of this study was to determine if the hyperexcitable conditions of zero Mg^{2+} and high K^+ can induce simultaneous intracellular and population bursting activities representing an *in vitro* seizure.

Methods: 600-µm-thick coronal brain slices were obtained from 9-15-day-old, CD-1 mice. Brain slices were submerged in a recording chamber under circulating ACSF ($32^{E\%}$ C, pH=7.4). Extracellular KCl ($[K^+]_o$) was elevated from 3 to 5 mM in both standard and zero Mg^{2+} ACSF. Population and intracellular recordings were performed by positioning the population electrode over cortical layers IV-V in close proximity to the intracellular electrode. In dual extracellular experiments, a second electrode was placed over layers II-III. Slices were perfused with zero Mg^{2+} ACSF for 30 to 180 mins, once or repeatedly.

Results: Under control conditions, neocortical rhythmic population activity, in ACSF containing 5mM $[K^+]_o$ had a frequency of 0.54 ± 0.22 Hz with an integrated burst area of 0.059 ± 0.027. Burst duration was 0.059 ± 0.054 s and bursts occurred at regular interval values between 0.47 ± 0.052 (n=16). Bath-application of zero Mg^{2+} -ACSF altered both ictal-like and inter-ictal-like population bursts. Ictal-like bursting was followed by periods of sustained network burst suppression. Compared to controls, neocortical network activity following treatment with zero Mg^{2+}-ACSF included up to four-times higher population burst durations and integrated burst area values during inter-ictal-like bursts, than during the ictal-like bursting, while burst regularity and frequency remained approximately the same. Repeated applications of zero Mg^{2+} -ACSF separated by 10-15 min. intervals resulted in quicker seizure-like activity initiation and rhythm synchronization. Simultaneous dual extracellular experiments, recording population activity from layers IV-V and II-III, revealed that layer II-III neurons can be recruited to burst synchronously by layer IV-V neurons. Some of the regular spiking neurons developed paroxysmal depolarization

shifts (PDS), or NMDA-dependent bursting activity upon initiation of seizure-like activity. In (n=3) neocortical slices oscillatory behavior consistent with "up-down" states was observed.

Conclusions: Our data suggest that high ($[K^+]_o$ /zero Mg^{2+} treatment can be used as a model of neocortical epileptogenesis and as a model for network plasticity. Further investigations are necessary to discover the underlying molecular mechanisms of seizure development and propagation.

3.055

ELECTROCHEMICAL ANALYSIS OF AN ACUTE SWINE MODEL OF CORTICAL EPILEPTIFORM ACTIVITY: ADENOSINE'S RISE AND FALL

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Rationale: Adenosine is a naturally occurring antiepileptic neurotransmitter. In acute animal models of epilepsy, adenosine administration aborts ongoing seizures. Further, microdialysis within the seizure focus demonstrates a post-ictal increase of adenosine 6 to 31 fold in human temporal lobe epilepsy. Adenosine's neurochemical dynamics, however, are not well understood peri-ictally due to the poor temporal resolution of microdialysis. Fast scan cyclic voltammetry (FSCV) is an electrochemical technique capable of measuring adenosine concentration changes on sub-second timescales. Here we use FSCV to investigate the peri-ictal temporal dynamics of adenosine in an acute model of seizures. We hypothesized that adenosine concentration increases during neocortical epileptiform activity in response to an acute chemoconvulsant.

Methods: White farm swine were used in an acute cortical model of epilepsy induced by penicillin injection (5500 Units). Electrophysiology was recorded from microelectrode arrays (Neuralynx Inc., bandwidth DC - 9 kHz, sampling at 32 kHz). Acute seizures were defined as synchronized continuous runs of epileptiform activity over 3.5 Hz. Wireless Instantaneous Neurotransmitter Concentration Sensor (WINCS) based FSCV was recorded using a triangular waveform from -0.4 to 1.5 Volts sampling at 10 times per second.

Results: Relative adenosine increase, as identified by unique FSCV oxidation peaks at approximately +1.5V and +1.0V (representing the first and second oxidation peaks of adenosine), occurs during and shortly after seizures. Average seizure duration was 26 ± 6 seconds. Time locked EEG and electrochemistry demonstrates an initial adenosine rise at 20 ± 9 seconds after electrographic seizure onset and peak adenosine level at 21 ± 10 seconds after seizure termination. The delay from the initial adenosine rise to seizure termination was -6 ± 9 seconds. Of these, the lowest variance was observed for the latency between seizure offset and adenosine rise, suggesting the adenosine rise may be associated with the termination of the seizure. The duration of seizure activity had a positive Pearson's correlation with adenosine rise duration (0.62).

Conclusions: WINCS based FSCV recording is capable of detecting extracellular adenosine concentration changes peri-ictally in this acute pig model of epileptiform activity. Simultaneous electrochemistry and electrophysiology show the least variance between initial adenosine increases and seizure termination, suggesting that adenosine rises at the termination of seizures.

3.056

ALTERATION OF WNT SIGNALING FOLLOWING STATUS EPILEPTICUS

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Rationale: Wnt signaling is an intracellular pathway well-studied in normal development and misregulated in cancers; it has recently been implicated in synaptic plasticity, but remains unexplored in the context of epilepsy. Our proposal investigates whether or not Wnt signaling is modulated following Status Epilepticus (SE). The overarching goal is modulating Wnt signaling as a novel treatment strategy for altering epileptogenesis at early time points immediately following SE.

In the canonical Wnt signaling, alteration of â-catenin protein is key. In absence of Wnt signals, Glycogen Synthase Kinase3â,(GSK3â), is a constitutively active kinase, which phosphoylates the N-terminal region of cytosolic â-catenin, leading to its ubiquitination and proteosome-mediated degradation. However, when Wnt is activated,these proteolytic processes are suppressed due to inhibition of GSK3â activity. Stabilized â-catenin is translocated into the nuclei where it associates with the transcription factor Tcf/Lef and activates gene transcription.

Methods: We utilized adult male Sprague Dawley Rats and age matched controls for this study. Status Epilepticus (SE) was induced using kainic acid 10 mg/kg I.P. and seizures scored according to a modified Racine Scale. Animals were sacrificed at 3, 12, 24 hours, 3 and 7 days to establish a time course for Wnt alteration.

Results: Our preliminary data suggested a modest increase in total â-catenin at 1 hour following SE. We added to this finding by examining additional time points.

Cytosol â-catenin n = 3-6 animals.

3hr 1.18±0.22

12hr 0.98±0.13

24hr 0.93±0.07

3d 1.06±0.19

7d 1.16±0.10

Nuclear â-Catenin

3hr 0.82±0.23

12hr 0.79±0.15

24hr 0.93±0.13

3d 1.19±0.37

7d 1.08±0.10

Conclusions: 1) There is not a significant increase in nuclear â-catenin following SE.

2) We are exploring explanations for this finding including the following possibilities:

2a) Changes in â-catenin are spatially specific (eg: CA1 vs CA3 vs Dentate Gyrus). We will subsegment these hippocampal regions to explore alterations in beta catenin levels.

2b) GSK3â is upstream of â-catenin and it's phosphorylation of â-catenin renders â-catenin inactive. We are exploring parallel changes in GSK3â in conjunction to changes in â-catenin.

3.057

COMPARISON OF ACUTE ELECTROGRAPHIC ABNORMALITIES IN A RAT MODEL OF HYPOXIA/HYPOXIA-ISCHEMIA

Andrew Zayachkivsky, M. J. Lehmkuhle, J. J. Ekstrand and F. E. Dudek (University of Utah, Salt Lake City)

Rationale: Hypoxic-ischemic (HI) brain injury is the most common cause of seizures during the neonatal period. Quantitative electrographic analyses in animal models are important for preclinical studies to develop new therapies for neonatal seizures. Here, a custom-built, miniature telemetry device was used to analyze acute seizures during either HI or hypoxia-alone treatment in neonatal rats. The hypothesis was that both of these treatments cause electrographic seizures during the acute hypoxic period, but only animals in the HI group develop cortical lesions with substantive neuronal damage.

Methods: The telemetry device was implanted on rat pups at postnatal day 6-7. Animals were allowed to recover for 24 h, and were then treated with HI or hypoxia alone. In the HI group, the left common carotid artery was cauterized before hypoxia. The pups were allowed to recover for 2 h with the dam, and were then treated for 2 h with 8% oxygen and 92% nitrogen (i.e., hypoxia) at 37°C.

Results: After carotid occlusion but before hypoxia, electrographic activity appeared normal in both the HI and hypoxia-alone groups. Animals (n=6 per group) in either the HI or hypoxia groups exhibited at least three distinct, abnormal forms of electrographic activity during hypoxia, including robust electrographic seizures of various durations. The average number of seizure events was similar across the groups (15.2 (± 2.3) after HI and 16 (±3.4) after hypoxia alone during the 2 h exposure). Histopathological analyses revealed that only animals with HI developed cortical lesions. Preliminary analyses showed few if any Fluro-Jade stained neurons (a marker for degenerating neurons) after the hypoxia-induced seizures, thus indicating that hypoxia-induced seizures (i.e., without ischemia) do not induce substantive brain damage.

Conclusions: Recent evidence (Kadam et al., 2010 J Neurosci 30:404) suggests that HI-treated neonatal rats without infarcts do not develop epilepsy. Here, both HI and hypoxia, induced intense seizures in immature rat pups. When combined with previous work (Kadam et al.,2010), these data suggest that neonatal seizures per se do not cause substantive brain damage, and hypoxia-induced neonatal seizures alone (i.e., without brain lesions) do not lead to epilepsy. The ability to record electrographic seizure activity during the neonatal period should enable quantitative analyses of seizures during the neonatal period to determine if they exacerbate other forms brain injury, and should also promote testing of novel therapeutic approaches for neonatal seizures during the early phases of perinatal stroke.

3.058

INVESTIGATING THE RISK OF SEIZURE AT HIGH FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION USING EPILEPTIC AND CONTROL NON-HUMAN PRIMATES

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Rationale: Trancranial magnetic stimulation (TMS)—a noninvasive, focal brain stimulation tool—activates brain regions functionally connected to the primary motor cortices, which maximally express the ictal discharge. In this study, we report our (preliminary) results of attempting to elicit paroxysmal responses with repetitive TMS (rTMS)—at different frequencies—in both epileptic and control groups.

Methods: Eight lightly anesthetized adult baboons (5 epileptics; 3 controls) underwent rTMS at stimulation frequencies of 3 Hz, 5 Hz, 10 Hz and 15 Hz. TMS pulses were delivered to each subject's primary motor cortex (M1) at 120% motor threshold for a total of 300 TMS pulses over a period of 90 seconds. The baboons were sedated using intravenous ketamine (5-6 mg/kg/hr) and paralyzed with vecuronium (0.1-0.3 mg/kg); the order of rTMS frequencies was randomized in each session. Scalp EEG recordings (Nihon-Kohden, Japan) were performed in order to evaluate any occurrence of epileptiform activity (ictal or interictal) triggered by rTMS. Electrodes were placed according to the Standard 10-20 International Electrode Placement System, and included FP1, FP2, T1, T2, O1 and O2, ground and reference electrodes, with electrode impedances of less than 10 micro-ohms. A board-certified clinical neurophysiologist reviewed all EEG recordings for epileptiform activity.

Results: Spontaneous generalized, interictal epileptic discharges (IEDs) were recorded in all five of the epileptic baboons prior to the rTMS study. No IEDs were noted in the EEG recordings of the 3 asymptomatic, control baboons prior to rTMS. We performed over 40 rTMS imaging studies in eight baboons, with each animal exposed to at least five rTMS protocols (greater than 1500 TMS pulses) per imaging session. Following every TMS pulse there was interference with the recording for about 3-5 seconds. Ringing artifacts were noted after 15 Hz stimulation in one epileptic baboon. Afterdischarges (2-3 for less than 2 seconds) were noted in one of five epileptic animals after continuous 3 and 5 Hz stimulation, which was morphologically distinct from the baboon's IEDs; no afterdischarges were observed in the control animals. No ictal discharges were recorded after any of the stimuli for any of the animals. Ictal and/or interictal discharges are likely to be generalized in this model and should have been recognized even by a limited set up.

Conclusions: Our study demonstrates that suprathreshold, high-frequency rTMS may be used to safely activate the motor cortex, even in subjects with a history of epilepsy. After delivering over 1500 TMS pulses in a single session, there was a very low risk of inducing a seizure as long as higher rTMS frequencies are delivered with longer intertrain intervals. Further studies are needed to investigate the parameters responsible for minimizing (or maximizing) the risk of seizure induction using rTMS.

3.059

ENHANCED EXCITABILITY AND EPILEPTOGENSIS ON HIPPOCAMPAL CA3 IN EL MICE

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Rationale: The aim of this study is to test the hypothesis that EL mice would show hyper-excitability which might cause the seizure susceptibility.

Methods: Experiment (Exp.) 1: We observed the changes in intracellular Ca2+ on adult EL and control DDY mice hippocampal slice after oxygen-glucose deprivation (OGD) using Ca2+ imaging with Rhod2-AM. Exp.2: We also performed the same experiments in developing animals (2-8w). Exp.3: We examined the changes in Ca2+ signal under the conditions of calcium free or applying of NMDA antagonist AP5 or AMPA antagonist CNQX. Exp.4: We observed the effect of growing up without acceleration in the developing period.

Results: Exp.1: In EL mice, cytosolic Ca2+ on CA1 and CA3 was significantly increased after OGD. Control DDY showed increase just on CA1 region. Exp.2: In developing EL mice, Ca2+ increase was less than the adults evenly in CA1 and CA3. The fluorescent intensity was successively increased in both CA1 and CA3 as it grows. Exp.3: Extracellular Ca2+ free condition, application of AP5 and CNQX partially decreased the intracellular calcium increase after OGD. Exp.4: In the mice without acceleration, the degree of Ca2+ increase in CA1 and CA3 was less than accelerated EL mice.

Conclusions: These results suggest that enhanced excitability on CA3 in EL mice might cause epileptogenesis. Hyper-excitability occurs gradually as they get older, not after growth and might be related with both glutamate NMDA and AMPA receptors.

3.060

FRONTAL CORTEX REQUIRES OPTIMAL PARVALBUMIN INTERNEURONS FOR SEIZURE PREVENTION AND COGNITION

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Rationale: Multiple epilepsies and seizure disorders are treated by pharmacologically increased GABAergic tone. Following successful control of the seizures with anti-epileptic drugs (AEDs), new cognitive side effects appear or previous deficits are not remediated. A main question in epilepsy is the cause of the impaired learning, the general lack of inhibition and/or the innate neural circuitry.

Methods: Neural recordings were obtained from awake transgenic mice with specific deficits in frontal lobe interneurons while performing cognitive tasks. Electrode arrays recorded single unit and local field potential activity during correct and incorrect trials and during the intertrial intervals. The local field potential activity was used as the surrogate for the EEG.

Results: Control mice demonstrated low baseline activity and increased signal in the delta range upon correct choices. In agreement with previous studies, the control mice made few errors and readily learned the tasks. Mice with decreased parvalbumin interneurons had difficulty learning the task, demonstrating increased numbers of errors. In absence of parvalbumin cells, the baseline of the local field potential showed increased power in the alpha range and overall increased amplitude. The signal:noise ratio in the mice with parvalbumin deficits was greatly reduced.

Conclusions: In addition to providing inhibition to stabilize the neural network and prevent seizure activity, parvalbumin interneurons assist in coding information required for proper learning. Perturbations in the neural network away from the optimum impaired cognition.

3.061

PHYSIOLOGIC SENSOR ARRAY TO IDENTIFY GENERALIZED SEIZURES IN CHILDREN IN A RESIDENTIAL SETTING

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Rationale: Caregiver intervention is the primary method for mitigating seizure-related adverse events but there exists no reliable method for detecting the occurrence of a significant seizure in the non-clinical setting. We sought to measure physiological responses that can arise from changes in autonomic nervous system activity in children with active epilepsy and to identify patterns that correlate with seizures but not with non-seizure behavior. The long term goal is to develop an effective wearable seizure monitoring and alert system that detects the occurrence of a generalized seizure 95% of the time with a false event rate of < 10%.

Methods: Three dependent children with drug-resistant epilepsy, age range 2-31, were enrolled into the study after parental consent. 1 child had tonic and tonic-clonic (TC) seizures several times a week, 1 child had myoclonic (MC) seizures several times per day, and one child had multiple seizure types, including tonic, TC, MC and partial seizures, several times per day. All 3 parents were given commercially available noninvasive and unobtrusive sensors that included heart rate, respiration, and torso orientation. One parent was also given a surface electromyography (EMG) sensor. Sensors were attached to the children multiple times for 1-24 hours over several months. Data were collected during over 50 seizure events. Enrollment of additional study subjects is ongoing and we are continuing to apply sophisticated digital signal processing algorithms to select the optimal array of noninvasive physiological sensors to meet the study goals. Electrocardiogram (ECG) patch electrodes are being added to the sensor array in July 2010 to monitor rhythm and detect cardiac arrhythmia associated with seizures. Collection of data on a vEEG unit will commence in the Fall of 2010.

Results: Example data from two seizure types are presented in Figure 1. The dotted lines denote the onset of the seizures as defined by caregiver observation. The analysis revealed multiple physiological changes that correlated with each seizure, including a rapid increase in heart rate, a rapid change in respiration rate and depth of breath (combined in the integrated respiration waveform), and a sudden change in torso orientation. Using cardiac parameters alone, our preliminary detection algorithm identified 7 out of 7 generalized tonic-clonic events and 15 out of 16 myoclonic events, for a detection rate of 94%. EMG data also differentiated seizure activity from normal activity. Seizure

onset was detected by a direction trend in muscle activity along the muscle fiber (Figure 2).

Conclusions: The data suggest that development of an effective monitor to detect generalized seizures in the home setting is possible and that detection of changes in the heart rate and rhythm should be key components. Such a system could have ground-breaking impact on the potential prevention of seizure-related injury, status epilepticus and SUDEP, as well as improvement of quality of life and increased independence for both caregivers and persons with epilepsy.

IMAGE: images/904919_A.jpg

IMAGE: images/904919_B.jpg

3.062

A CLOSED-LOOP IMPLANTABLE DEVICE FOR EPILEPTIC SEIZURE DETECTION AND NEUROSTIMULATION

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Rationale: Some patients with pharmacoresistant partial epilepsy are not candidate for surgery. There has been growing interest in neuro-responsive intracerebral local treatment of seizures such as focal drug delivery, focal cooling, or electrical stimulation. The latter requires an effective seizure-detection system and a brain stimulator. We present a low-power implantable integrated device for responsive electrical stimulation.

Methods: The proposed implantable closed-loop neuro-stimulator (CLNS) combines an epileptic seizure detection (EPSD) with simultaneous electrical stimulation feedback. The EPSD provides continuous long-term monitoring of intracerebral EEG (iEEG). The sensitivity of EPSD is enhanced and several decision boundaries are introduced to reduce the number of false alarms for the patient-specific seizure pattern. The seizure-onset information is extracted through early modulation and proper rectification of the intracerebral signal. The EPSD determines the high-frequency patterns and the progressive amplitude increase of the seizure signal. The iEEG is analyzed over a certain time frame and a higher number of the detection indicates an upcoming seizure event.

Results: The EPSD algorithm was validated through behavioral simulations in MATLAB. The EPSD was implemented and fabricated in a 0.18-µm CMOS technology. The EPSD circuits fit in 2 mm X 1 mm chip area. Mixed-mode (analog/digital) tuning circuitry was used to enable adjusting the amplitude threshold and the time frame of the seizure-onset detection. Thus, this EPSD chip can be adapted to the patient' specific seizure onset pattern. Furthermore, it can be tuned to be non-responsive to high-frequency brief electrical seizures if needed. This EPSD chip demonstrated accurate detection of seizure onsets, based on iEEG recordings from 8 patients with epilepsy. Furthermore, the influence of low-frequency noise was found to be negligible. Moreover, the total power dissipation was less than 6.80 µW. The electrical stimulator has been highly miniaturized. The external controller provides energy and transmits data to the implanted stimulator by means of inductive coupling of spiral antennas. The control unit of the implanted stimulator is based on a commercially available Field Programmable Gate Array (FPGA) that present advantageous low-power and small-scale features. The CLNS is assembled on two circular printed circuit boards (PCB) of 2 cm diameter each, which are connected together with a flexible bus connector. The power consumption of the CLNS has showed that the system could run on a button cell battery for more than 8 years.

Conclusions: The experimental results demonstrated the detection accuracy and the low-power dissipation of this implantable CLNS.

3.063

MOUSE EMBRYONIC STEM CELL-DERIVED PYRAMIDAL NEURONS ARE ABLE TO SURVIVE IN A KAINIC ACID CORTICAL LESION AND IN A SCLEROTIC HIPPOCAMPUS

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Rationale: Like other neurodegenerative disorders, epilepsy is characterized by neuronal loss. Temporal lobe epilepsy is the most common form of difficult to treat epilepsy and is frequently associated with hippocampal sclerosis, a lesion characterized by reactive gliosis and loss of pyramidal- and interneurons in specific hippocampal cell layers. Replacement of lost cells seems to be a vital step for functional repair of the brain. A promising technique for replacement of lost cells is neurotransplantation. This technique tries to repair damaged neuronal networks or to deliver anti-epileptic substances by means of cell transplantation. In this study we evaluate if predifferentiated pyramidal neurons, derived from mouse embryonic stem cells, are able to survive in a kainic acid (KA) cortical lesion and in the sclerotic hippocampus of the intrahippocampal KA status epilepticus mouse model.

Methods: In vitro generated tau-Green Fluorescent Protein (GFP) mouse embryonic stem cells were differentiated to precursors of pyramidal neurons and transplanted in a cortical and hippocampal lesion induced by focal injection of KA three days before grafting. In a first experiment, a cortical lesion was induced in mice by focal injection of 200 ng KA in 50 nl saline. Three different cell numbers were transplanted in the lesion [1,000 (n=4); 5,000 (n=6) and 25,000 cells (n=6) in 0.5µl medium]. In a second experiment an intrahippocampal lesion was induced by focal injection of 100 (n=5) or 200 ng KA (n=4), dissolved in 50 nl, saline and 700 cells in 0.5µl medium were grafted in the sclerotic hippocampus. Four weeks after transplantation mice were transcardially perfused to evaluate the presence of GFP-positive neuronal projections from grafted cells.

Results: In the first experiment, a dense network of projections were found in KA lesioned cortex, in 5 out of 6 mice grafted with 25,000 cells, in 4 out of 6 mice grafted with 5,000 cells and in 1 out of 4 mice grafted with 1,000 cells. A high number of axonal projections, running down along the lower layers of the cortex and along the external capsule, were seen. These projections were strikingly similar to the projections of the endogeneous cortical neurons.

In the second experiment, a dense network of GFP positive neuronal projections were found in the sclerotic hippocampus in 3 out of 4 mice, injected with 200 ng KA, and in 2 out of 5 mice, injected with 100 ng KA. The projection pattern of grafted neurons was very similar in the successfully grafted mice. GFP positive neuronal fibers were confined to the ipsilateral and contralateral hippocampus and found in all layers of the hippocampal formation.

Conclusions: These promising results show that mouse embryonic stem cells, in vitro predifferentiated to pyramidal neurons, are able to survive in a KA cortical lesion and in a sclerotic hippocampus. Further research will be done to determine the functional integration of the grafted neuronal precursors.

3.064

ON-DEMAND PULSATILE INTRACEREBRAL DELIVERY OF CARISBAMATE CONCURRENT WITH CLOSED-LOOP DIRECT NEUROSTIMULATION THERAPY IN A SELF-SUSTAINED LIMBIC STATUS EPILEPTICUS (SSLSE) RAT MODEL

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Rationale: The goal of this work is to establish the feasibility of ameliorating spontaneously recurring limbic seizures with closed-loop direct neurostimulation therapy in tandem with on-demand pulsatile intracerebral delivery of the novel antiepileptic drug (AED) carisbamate (Johnson & Johnson Pharmaceutical Research and Development).

Methods: Twenty Fischer344 male rats (5 animals/group) were used. Stereotactic coordinates were chosen to guide a customized 16-contact dual fluidic-recording microelectrode shaft (NeuroNexus Technologies) into the right dorsal dentate gyrus (DG), and a 16-contact non-fluidic microelectrode shaft into the left dorsal DG. A stainless steel Teflon-coated twisted bipolar electrode was stereotactically placed in the medial division of the right perforant path (PP) 8mm posterior to bregma. Evoked potentials were used to confirm placement of all electrodes. Following a 6 day post-implant recovery period, a 1hr baseline electrocorticogram was acquired. Each animal then underwent a 90min electrical SSLSE protocol, inducing spontaneous limbic seizures. A line length signal processing algorithm (DataWave Technologies) was used to detect electrographic ictal onsets recorded from the distal eight serially arranged contacts in the right DG. Successful detection of this pattern automatically triggered delivery of stimulation therapy parameters (50uA less than the afterdischarge current, 1ms pulse duration, 100ms train duration at 50Hz). Subjects were designated to receive focal stimulation therapy delivered through the right PP either in the presence or absence of a 20nl [14C]-carisbamate bolus (rate=500nl/min) The AED was delivered in the right DG. In addition, a group received direct delivery of carisbamate alone. A final group received stimulation therapy concurrent with vehicle only. Each animal was sacrificed and brain tissue immediately frozen after an 8hr therapy session. [14C]-sensitive film was exposed to 10um tissue sections and developed 28 days later to determine AED distribution. Frequency and duration of ictal runs were assessed by a blinded evaluator reviewing the entirety of the electrocorticography with video.

Results: Preliminarily, direct neurostimulation therapy delivered in the PP can abort an ictus detected at a distance in either ipsi- or contralateral DG. In addition, a trend is seen of a decreased frequency of ictal runs in those subjects receiving closed-loop direct neurostimulation therapy in tandem with on-demand intra-parenchymal carisbamate delivery, compared to closed-loop stimulation therapy alone.

Conclusions: 1) Closed-loop detection of the ictal onset at a distance from axonally-connected delivery of direct stimulation therapy can stabilize an active epileptic circuit. 2) On-demand delivery of nanobolused intraparenchymal carisbamate is a promising strategy for augmenting closed-loop direct stimulation therapy in a rat model of spontaneously recurring limbic seizures.

Supported by a grant from Ortho-McNeil Janssen, LLC

3.065 – This poster has been changed to Platform A.09

3.066

POISSON DISTRIBUTED HIGH FREQUENCY HIPPOCAMPAL STIMULATION SUPPRESSES EPILEPTIC SEIZURES IN THE KAINATE RAT MODEL

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Rationale: Temporal lobe epilepsy (TLE) remains one of the most difficult to treat forms of epilepsy. One third of the patients is or becomes refractory to anti-epileptic drugs, emphasizing the need for new therapeutic strategies. Hippocampal Deep Brain Stimulation (DBS) is a promising experimental approach, shown to be effective in both animal models of epilepsy as in patients suffering from TLE. However, optimal stimulation paradigms are still to be resolved. In this study we demonstrate the efficacy of a new stimulation paradigm: Poisson distributed stimulation (PDS) in the kainic acid model, a validated model for human TLE.

Methods: Status epilepticus (SE) was induced by intraperitoneal injection of kainic acid (2-5 injections of 5mg/kg). More than fifty days following SE, rats (n=24) with spontaneous seizures were implanted with depth stimulation- and recording electrodes in the hippocampus. After 15 days of continuous baseline EEG monitoring, rats were randomly assigned to one of two treatment groups. One group (n=13) received continuous PDS (mean frequency of 130 Hz but with Poisson distributed, asynchronous, interpulse intervals) and 11 received regular, synchronous, High Frequency Stimulation (HFS at 130 Hz) during the following 10 days. Seizure frequency and seizure duration were continuously monitored before, during and after 10 days of continuous DBS. Stimulation intensity was 100μA below the threshold for induction of epileptiform EEG activity.

Results: Seven out of 13 rats (54%) treated with PDS and 5 out of 11 rats (45%) treated with HFS experienced a significant reduction in seizure frequency. In them seizure frequency was reduced to 33% of baseline ($p<0.01$) during PDS and to 50% of baseline ($p<0.01$) during HFS. None of the stimulation modalities affected mean seizure duration. After termination of the stimulation, the effect induced by PDS faded away in days restoring seizure frequency to its pre-stimulus levels. The other 12 non-responder rats did not demonstrate any reduction in seizure frequency. The maximum stimulus intensity at which rats could be stimulated without experiencing EEG and/or behavioral side effects was significantly lower for PDS than for HFS ($p<0.02$).

Conclusions: We conclude that continuous hippocampal PDS with a mean frequency of 130 Hz is an interesting new stimulation paradigm, which significantly reduces spontaneous seizure frequency in a large fraction of the epileptic rats. Its efficacy, even at a lower stimulus intensity, is larger than that of the equivalent regular HFS at 130 Hz.

3.067

EFFECT OF TRANSCUTANEOUS ELECTRICAL STIMULATION ON PENTYLENETETRAZOLE-INDUCED SEIZURE ACTIVITY SYNCHRONY IN BETA AND GAMMA BANDS IN RATS

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Rationale: Epilepsy is a neurological disorder that affects approximately one percent of the world population of which 75% are from developing countries. Anti-epileptic drugs are ineffective in 25-30% of the epileptic patients. Electrical stimulation to control seizures may be an additive therapy which has shown promise in ongoing research.

Methods: Ten Sprague-Dawley rats were used in the current study. Three custom designed tri-polar concentric ring electrodes were placed on the scalp with conductive paste and adhered using dental acrylic cement. Seizures were induced with pentylenetetrazole (PTZ) and EEG signals were recorded. Three animals were used as controls with the other seven receiving noninvasive transcutaneous electrical stimulation (TcES). The seizure synchronous activity was measured by coherence in the EEG recorded between electrodes.

Results: The controls showed a significantly increased beta-gamma activity synchrony after PTZ injection and gradually increased even further with time compared to baseline beta-gamma activity. This beta-gamma activity synchrony during seizures was significantly reduced similar to the baseline recordings after treating the rats with TcES. The noninvasive TcES was able to significantly reduce ($p<0.01$) seizure activity synchrony.

Conclusions: The beta/gamma electrographic activity can be detected on the scalp surface of seizing rats with tripolar concentric ring electrodes. Our data shows that TcES reduces pathologically increased synchrony at beta/gamma frequencies and this may contribute to the TcES ability to reduce or eliminate seizures caused by PTZ as well as other convulsants, as we have demonstrated previously.

3.068

MUSCIMOL-DELIVERING SUBDURAL PHARMACOTHERAPY DEVICE FOR THE TREATMENT OF INTRACTABLE NEOCORTICAL EPILEPSY: PRELIMINARY SAFETY AND EFFICACY STUDIES IN FREELY-BEHAVING BONNET MACAQUES

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Rationale: Subdural pharmacotherapy is a novel strategy for the treatment of intractable focal neocortical epilepsy (Ludvig et al., 2009, Epilepsia 50:1528-1167). For this strategy, we developed a triple-function subdural strip able to (1) deliver drugs transmeningeally, (2) remove neocortical cerebrospinal fluid [CSF], and (3) record local EEG activity (US patent pending). The functions of the strip are regulated by a control unit comprising a dual minipump, a microprocessor, a signal conditioner, a radiofrequency (RF) transceiver and a battery. This is the first safety and efficacy report on the long-term use of this system in nonhuman primates.

Methods: Adult bonnet macaques (Macaca radiata; n = 2) were implanted with the subdural strip and its control unit. The strip was placed over the right frontal cortex, and connected to the control unit secured to the cranium. An additional subdural EEG electrode was placed in the contralateral area. In monkey 1, intermittent saline delivery (40 microliter/delivery at 12-hour intervals) started immediately after implantation. In monkey 2, similar delivery alternated with neocortical CSF removal (20 microliter/removal at 6-hour intervals). After a 2-month observation period, the control unit was modified to deliver a seizure-inducing concentration of acetylcholine (Ach, 200 mM) through the strip and subsequently deliver 1 mM muscimol in the same way. The monkeys were behaving freely during this test. Before this test, and after this test for up to 4 months, the behavior of the monkeys and the EEG activity of their implanted frontal cortices were monitored daily.

Results: Before and after the subdural drug delivery test, the monkeys displayed no abnormal behavior or neurological symptoms. Artifact-free EEG recording from the implantation site was maintained throughout the study (Fig. 1A). In the monkey subjected to intermittent saline delivery only, the minipump tubing was clogged 1.5 months after implantation. In the monkey subjected to alternating saline delivery and CSF removal the minipump tubing was not clogged, allowing drug delivery. Subdural Ach induced EEG seizures localized to the ipsilateral implantation site, with the contralateral cortical EEG unaffected (Fig. 1B). Behavioral monitoring revealed contralateral clonic movements only. Subsequent muscimol delivery into the Ach-induced acute seizure focus terminated the EEG seizure (Fig. 1C). Similar pharmacological data could be obtained in the monkey with the clogged apparatus only after manual cleansing of the tubing.

Conclusions: This preliminary study suggests that (1) local CSF removal may be necessary to maintain the long-term functional integrity of subdural drug delivery strips, (2) muscimol-delivering subdural strips can be used to control focal neocortical seizures, and (3) the long-term use of subdural implants for combined fluid-delivery, fluid-removal and EEG recording does not seem to be harmful. Support: Epilepsy Research Foundation grant #140929 to N.L.

IMAGE: images/903804_A.jpg

Fig. 1. Wireless frontal cortical EEG recordings from a freely-moving bonnet macaque implanted with the subdural triple-function strip in the right frontal cortex. (A) Baseline EEG. (B) Focal EEG seizure in the area of the strip [ch. 1-3] with no EEG seizure in the contralateral area [ch. 4] after Ach delivery via the implant. (C) Cessation of the Ach-seizure after the delivery of 1 mM muscimol into the seizure focus via the implanted subdural strip.

3.069

CONVECTION-ENHANCED DELIVERY OF LEVETIRACETUM FOR TREATMENT OF EPILEPSY

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Rationale: Resection of epileptogenic tissue is a standard method in the surgical treatment of epilepsy. However, respective surgery is not recommended when the epileptogenic lesion overlaps functionally

eloquent area. For such cases, “non-resective” surgical treatments, such as multiple subpial transection or vagal nerve stimulation, are considered although its efficacy is fairly inferior to respective surgery. Thus, a new method for non-resective control of epileptic lesion is highly awaited. Convection-enhanced delivery (CED) is a method of delivering drugs from thin catheter tip directly into brain parenchyma with slow infusion rate. This method can achieve larger drug distribution volume and less damage than bolus injection. CED is already in clinical use for treatment of malignant brain tumors. Levetiracetam (LEV) is characterized by its hydrophilic character which is suitable for long-lasting distribution in the interstitial space of brain. In this study, we evaluated the safety and efficacy of LEV-CED for rat epilepsy model.

Methods: Hippocampal epilepsy model was prepared by injecting 50ng tetanus toxin into the right ventral hippocampus of Wister rat (n=5). After the development of spontaneous seizures, LEV was delivered by CED (concentration: 100ìM, injection rate: 0.5ìl/min, total injection volume: 5ìl) to the epileptic hippocampus under the anesthesia with ketamine and xylazine. Local field potentials were simultaneously recorded from depth electrode inserted to the hippocampus. The average number of spikes in 10 minutes were statistically compared between pre- and post-CED. Toxicity of LEV-CED was examined histologically for various concentrations (32, 100, 320, 1000ìM) using normal Wister rat (n=3 for each group).

Results: The average number of spikes decreased after LEV-CED with statistical significance (Figure, $p<0.001$). No tissue damage was observed histologically in any group.

Conclusions: LEV-CED has significant suppressive effect to epileptic discharges in rat tetanus toxin model and no histological damage was observed in any concentrations tested. CED can be a candidate of new method for “non-resective” surgical treatment of intractable epilepsy.

IMAGE: images/904777_A.jpg

3.070

VAGUS NERVE STIMULATION-INDUCED INCREASE IN HIPPOCAMPAL NORADRENALINE LEVELS IS RESPONSIBLE FOR THE CONTROL OF LIMBIC SEIZURES

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Rationale: Vagus nerve stimulation (VNS) is an adjunctive treatment for patients with refractory epilepsy. Drawbacks of this treatment are the lack of responder identification and knowledge of the mechanism of action. The aim of this study is to unravel the potential mechanism of action by screening of the VNS-induced changes in hippocampal neurotransmitters in relation to the limbic seizure suppressing action of this treatment in the intrahippocampal pilocarpine model.

Methods: Rats were stereotactically implanted with a guide cannula and a bipolar electrode in the hippocampus and a stimulation cuff-electrode around the left vagus nerve. VNS was performed in all rats using the following stimulation parameters: 30 Hz, 1 mA, 250 µsec, 7 sec ON-18 sec OFF. This was combined with intracerebral microdialysis to measure hippocampal noradrenalin, dopamine, serotonin and GABA concentrations and to evoke limbic seizures by intrahippocampal administration of pilocarpine. Clinical and electrographic seizure activity was identified using video-EEG monitoring. In this way the effect of VNS on hippocampal neurotransmitter levels and pilocarpine-induced seizure activity was assessed. In a second set of experiments the importance of the VNS-induced noradrenergic stimulation to its seizure-suppressive effect was evaluated by co-administration of SKF 86466, a noradrenergic á2-receptor antagonist.

Results: VNS significantly increased the latency between the start of the pilocarpine infusion and the onset of epileptiform discharges. It also significantly attenuated duration of pilocarpine-induced seizures and reduced clinical seizure severity. Neurochemically, VNS significantly increased extracellular hippocampal noradrenalin levels. A highly significant positive correlation was found between the noradrenergic and seizure-suppressive effects of VNS. Selective blockade of noradrenergic á2-receptors completely reverted the seizure-suppressive effects of VNS in the intrahippocampal pilocarpine model.

Conclusions: VNS has seizure-suppressing effects in the intrahippocampal pilocarpine model for limbic seizures as a result of an increase in hippocampal noradrenalin concentration induced by VNS. Increased noradrenalin concentration is a promising biomarker for the evaluation of anti-seizure effects of VNS.

3.071

CONTROL OF A VISUAL KEYBOARD USING AN ELECTROCORTICOGRAPHIC BRAIN-COMPUTER INTERFACE

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Rationale: A brain-computer interface (BCI) is a system that allows individuals with severe neuromuscular disorders to communicate and control devices using their brain waves. Over two million people in the USA may benefit from assistive devices controlled by a BCI. Disabled subjects have used scalp EEG-based BCI paradigms to reliably control personal computers. Electrocorticography (ECoG) has also recently been demonstrated to be a viable control signal for a BCI. The current EEG signals used to operate our visual evoked BCI paradigm have not been characterized in ECoG. We hypothesize that ECoG-translated BCI control signals will provide superior speed and accuracy over scalp-recorded EEG for the symbol selection matrix paradigm.

Methods: Subjects:

Six patients with medically refractory epilepsy undergoing Phase 2 intracranial grid and depth electrode monitoring for seizure localization were studied.

Data Acquisition and Task:

Concurrent with the clinical ECoG recording, a 16- or 32-channel subset of each patient’s electrodes was monitored using a separate EEG amplification system and BCI2000 software. Each patient sat approximately 75 cm from a video screen with a 6 X 6 square matrix of alphanumeric characters displayed. The task was to focus attention on a prescribed character from the matrix and silently count the number of times the prescribed character randomly flashes until a new character is specified for selection. All data was collected in the copy mode: a

character string is presented on the top left of the video monitor and the current prescribed character is highlighted at the end of the character string. A single session was conducted without feedback to the user. The session consisted of 8-11 experimental runs; each run is composed of a series of characters that form a word as chosen by the investigator. There were 32-39 character epochs total in a session.

Data Analysis:

For each patient, data from the first four runs were preprocessed and used to train a linear classifier using Stepwise Linear Discriminant Analysis (SWLDA). This classifier was tested using the four subsequent runs to determine the classifier's ability to predict the intended target from independent data.

Results: This is a preliminary analysis of an ongoing study. The classifier was able to predict the intended target character with an average accuracy of approximately 90% across subjects. The maximum communication rate corresponding to the average accuracy is 12 bits per minute and 14 seconds per selection. Four of the six subjects achieved communication rates in excess of 17 bits per minute corresponding to less than 14 seconds per selection.

Conclusions: These preliminary results indicate that a potentially superior BCI communication rate can be achieved using ECoG signals compared to scalp-recorded EEG signals. Further improvements may be realized by systematic characterization of the ECoG responses.

3.072

RAPID TERMINATION OF IN VIVO NEOCORTICAL SEIZURES BY PHOTORELEASE OF GABA WITH A BLUE LIGHT EMITTING DIODE

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Rationale: We previously demonstrated that a low concentration of a new caged GABA, ruthenium-bipyridine triphenylphosphine-GABA (Rubi-GABA), when illuminated by blue light, released sufficient GABA, to reduce seizure-like activity in brain slices. In a new set of experiments, we tested Rubi-GABA and a blue light emitting diode (LED) as a potential therapy for neocortical epilepsy in vivo.

Methods: Adult male Sprague-Dawley rats were anesthetized with isofluorane. We placed two screw electrodes symmetrically over each hemisphere and differentially recorded the electroencephalogram (EEG). After creating a 4 mm diameter cranial window over the left hemisphere, we carefully opened the dura and created a reservoir with dental cement around the cranial window to allow administration of artificial cerebrospinal fluid (ACSF) on the brain surface. The control and experimental group rats were pretreated by applying 200 µl ACSF or ACSF containing 5 µM Rubi-GABA, respectively, on the brain surface for one hour. We then induced focal neocortical seizures by switching to fresh pretreatment solution containing 500 µM 4-aminopyridine (4-AP) for both groups. An LED (emission maxima of 470 nm) was glued to the end of a copper rod and placed just above the cranial window allowing unfocused light to directly illuminate the brain surface. A TTL pulse controlled the LED. The effect of one minute illumination (500 mA) at seizure onset was compared in the absence and presence of 5 µM Rubi-GABA.

Results: LED illumination had no effect on seizure duration in the absence of Rubi-GABA. Seizure durations in the absence of Rubi-GABA, with and without light flashes, were 159±32 seconds and 160±58 seconds, respectively ($P>0.05$;N=8 rats). In the presence of 5 ìM Rubi-GABA without illumination, seizures were slightly, but insignificantly prolonged to 180±88 seconds ($P>0.05$;N=8 rats). However, the seizures were reduced to 41±24 seconds ($p<0.01$;N=8 rats) with illumination in the presence of 5 uM Rubi-GABA (see figure below).

Conclusions: Illumination of Rubi-GABA with a blue LED uncages sufficient GABA to rapidly terminate severe experimental focal neocortical seizures. Because the Rubi-GABA is activated with visible light, there is greater tissue penetration and less photo-toxicity than with UV-sensitive caged compounds. We believe that it should be possible to integrate a small LED with a subarachnoid drug delivery pump and seizure detection algorithms to create an implantable device for the treatment of human epilepsy. The temporal and spatial resolution of optical techniques make this a potentially attractive approach for the therapy of focal epilepsy

IMAGE: images/905783_A.jpg

Figure. A. In vivo seizure in rat neocortex after subdural application of 4-aminopyridine. Rubi-GABA (5 µM) was present but there was no illumination. B. Seizure in the same Rubi-GABA -treated rat showing that 473 nm light applied for 60 s, dramatically shortened seizure. Calibration identical for A and B.

3.073

EVALUATION OF STATNET DEVICE FOR RAPID EEG RECORDINGS

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Rationale: An EEG is important to diagnose non-convulsive status epilepticus and to distinguish convulsive SE from psychogenic SE. Delays in the diagnosis and treatment of SE or inappropriate treatment for convulsive SE in the setting of psychogenic SE may result in increased morbidity and mortality. Currently, an EEG is often difficult to obtain due to lack of technologist availability, particularly at night, and the typical setup is time consuming. Thus, a system which can be rapidly applied by a non-EEG technologist is highly desirable. The StatNet device is a lightweight, reduced set of electrodes with a self-adhesive backing that can be quickly applied by untrained personnel and may potentially hasten the diagnosis of SE. The purpose of this study is to assess the performance of the StatNet device for EEG recordings.

Methods: Twenty patients who demonstrated frequent focal or generalized EEG abnormalities, such as slowing or epileptiform activity, while undergoing a conventional EEG were enrolled in the study. At the end of their conventional EEG, subjects then had an additional 10-minute EEG recording using the StatNet electrode set. Both EEG recordings were then reviewed by four board-certified neurophysiologists in a blinded fashion, and assessed using the following parameters: quality of recordings, duration of artifacts (electrode, electrical, movement, and muscle artifacts), and ability to detect abnormal findings, such as epileptiform discharges, electrographic seizures, and focal or generalized slowing. The set up time for both types of electrodes was compared.

Results: No difference was noted in the quality of the recordings or the duration of artifacts between the StatNet and the conventional EEG group. The mean setup time was 7.18 minutes for the StatNet group and 22.44 minutes for the conventional group and the difference was statistically significant ($p<0.0001$). None of the studies with clear epileptiform activity (focal or generalized spike-and-wave or polyspike-and-wave activity) were misinterpreted using the StatNet electrodes. Both inter-rater and intra-rater variabilities were noted with respect to the location and presence of focal or generalized slowing. A penalty factor was assigned to studies for which the StatNet reading differed from that of the conventional recording. After this adjustment, a two-sample t-test yielded statistically significant time advantage using the StatNet device ($p=0.017$).

Conclusions: The StatNet electrode set represents a faster and easier method of obtaining high quality EEG recordings that are comparable to those using conventional electrodes. The device also has the potential for widespread use since application by trained personnel is not essential. Thus, it may be a more desirable alternative to conventional EEG electrodes and may be more suitable for use in emergency settings, such as the emergency room, the intensive care unit, or even in pre-hospital settings, where rapid diagnosis of SE is critical. Further research is needed to evaluate of the performance of the StatNet electrodes and the clinical impact of their use in these emergent situations.

3.074

CHANGES IN EFFICACY OF VAGUS NERVE STIMULATION (VNS) OVER TIME: REVIEW OF 65 CONSECUTIVE PATIENTS WITH TREATMENT-RESISTANT EPILEPSY TREATED WITH VNS e" 10 YEARS

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Rationale: Some centers have reported an improvement in seizure control over time with vagus nerve stimulation (VNS). However, most reported studies are prone to methodological biases secondary nonresponder attrition (declining-n) or the imprecision of last visit carried forward analyses. We analyzed the efficacy of VNS over time in a series of 65 consecutive patients with focal and generalized treatment-resistant epilepsy (TRE) who underwent VNS therapy for 10 or more years.

Methods: A retrospective review was performed on 436 consecutive patients with TRE who underwent primary VNS implantation by the senior author between 1997 and 2008. Sixty-five patients (29 females/ 36 males) had undergone VNS therapy for at least 10 years and are the subjects of this report. The mean age at VNS insertion was 30.0 years (range: 6.7 to 73 years) and included 44 adults (e" 18 years; 67.7%) and 21 children (32.3%). Seizure frequency and anti-epileptic drug (AED) regimens were recorded prior to VNS and following VNS insertion at 6 months, 1 year, 2 years and every 2 years thereafter.

Results: Prior to VNS insertion, the mean weekly seizure frequency was 10.8±24.0 and patients were taking an average of 3±0.6 AEDs. The mean duration of VNS therapy for this group was 10.4 years (range: 10.0 to 11.6 years) and the mean decrease in seizure frequency at last follow-up was 76.3%. The mean percentage seizure reduction at 6 months and years 1, 2, 4, 6, 8 and 10 years was 35.7%, 52.1%, 58.3%, 60.4%, 65.7%, 75.5% and 75.5%, respectively. Seizure frequency was significantly reduced from baseline at each of the recorded intervals ($p<0.001$) and significant improvements in seizure control were seen between 6 months and 1 year, 1 year and 2 years and years 4 to 6. There was no difference in seizure control between years 2 to 4 years or 6 to 10 years. Four patients had intracranial surgery (callosotomy X 2, brain tumor, cavernoma) after VNS implantation. Two patients underwent device removal and reinsertion after craniotomy and 1 patient had device removal with subsequent increase in seizure frequency. Two patients died from causes unrelated to epilepsy during the follow-up period. There was no significant difference in number of AEDs at any period during follow-up but changes in AED regimens were noted at most interval follow-up visits. Alterations in the device stimulation parameters were common as well, but less frequent than AED changes.

Conclusions: Following an initial "ramp-up" period and accommodation throughout the first year or 2 following VNS implantation, seizure control tended to improve slightly throughout the 10 years of therapy and eventually stabilize. Variation in seizure frequency, however, was common in this population and frequent changes in AED regimens or stimulation parameters were important and possibly synergistic components of seizure control.

3.075

SURGICAL TREATMENT OF THE PATIENTS WITH RASMUSSEN'S ENCEPHALITIS (20 CASES)

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Rationale: Presenting of 20 cases with Rasmussen's encephalitis(RE) being surgically treated, to observe the clinical effects after 3 to 54months follow-up.

Methods: Retrospectively analyze the clinical data of 20 cases with RE in our epilepsy center from April 2004 to June 2009. Of the 20 cases, 9 were males and 11 were females. The age of onset was from 1.7 to 17 years (average 5.7) and disease duration of 5 months to 12 years (average 3.6). Different operations had been made based on the pre-operation evaluations (Adame's Modified hemispherectomy, functional hemispherectomy, hemispherotomy and selectively epileptogenic zone resection. Regular follow-up of all cases after operation was made.

Results: 4 cases were operated with Adame's Modified hemispherectomy (AH), 10 case were operated with functional hemispherectomy(FH) and 5 cases with hemispherotomy, 1 cases with selectively epileptogenic zone resection. During 3 to 54 months follow-up, 16cases had seizure free (Engel I, 80%) , 3 cases with alleviation of seizures (1 cases with Engel class II and 1 with Engel class III), 1 case had frequent seizures after operation(probably bilateral RE). After operation, most patient are able to walk without the use of assistive devices except one case, but the fine motor hand movements were lost.

Conclusions: RE is a drug-resistant epilepsy syndromes accompanied by progressive neurological deterioration. Hemispherectomy is a viable alternative, which should be considered in the treatment of RE based on the pre-evaluations, various operation methods (AH, FH, hemispherotomy) don't influence seizure outcome, but the long-term effect remains to be observe.

3.076

STATUS EPILEPTICUS IN A VETERAN POPULATION: CAUSES, TREATMENT APPROACHES AND OUTCOMES IN 72 PATIENTS

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Rationale: Status epilepticus (SE) is a medical and neurologic emergency. Optimal treatment approaches are not clearly defined and outcomes are often poor. To better understand SE causes, treatment approaches, and associated outcomes, we retrospectively reviewed all cases of SE treated at the Veterans Affairs Greater Los Angeles Healthcare System (VA WLA) over a period of 8 years.

Methods: SE cases were identified via an electronic electroencephalogram (EEG) consult service tracking list from July 1, 2001 to June 30, 2009. Four-thousand five-hundred and nine EEG reports were reviewed and 72 cases of SE were identified. Causes of SE, efficacy of treatments used, and outcomes were assessed.

Results: The most common causes of SE included anoxic/hypoxic injury (21%), cryptogenic/idiopathic etiologies (15%), traumatic brain injury (13%), and anti-epileptic drug (AED) non-adherence (11%). Lorazepam was the most frequently used first-line AED and was successful in terminating 24 of 54 SE cases (44%) when used first-line. Lorazepam followed immediately by phenytoin was used in only 5 cases as initial treatment and was successful in only 2 cases (40%). The mortality rate for SE overall was 31%.

Twenty-two of 72 cases (31%) were refractory to two or more AEDs and considered to be refractory SE (RSE). The most common causes of SE in refractory cases did not significantly differ from that of medication-responsive patients and included anoxic/hypoxic injury (27% versus 18%), cryptogenic/idiopathic etiologies (13% versus 16%), traumatic brain injury (18% versus 10%), and AED non-adherence (9% versus 12%). Lorazepam, phenytoin, and propofol were the most frequently used antiepileptic drugs in RSE. Lorazepam was successful in terminating RSE in 9 of 19 cases (46%), phenytoin was successful in terminating RSE in 2 of 17 cases (12%), and propofol was successful in terminating RSE in 4 of 11 cases (36%). Other commonly used agents in RSE were midazolam, levetiractam, and phenobarbital which were effective in terminating RSE in 25%, 22% and 67% of cases respectively. As expected, RSE was associated with higher mortality than non-RSE cases (55% vs. 20%).

Conclusions: Causes of SE in the veteran population are highly variable. Lorazepam continues to be one of the most effective AEDs in both medication-responsive SE and RSE. Phenobarbital, propofol, and midazolam may be the most effective agents in RSE after failure of lorazepam. Overall mortality rate in our SE cohort was similar to what is reported in the literature. However mortality rate for our RSE cohort were worse than what is reported in the literature, likely due to increased age and greater number of comorbidities associated with our veteran patients.

3.077

REFRACTORY STATUS EPILEPTICUS IN CHILDREN: CLINICAL AND CONTINUOUS ELECTROENCEPHALOGRAM MONITORING CHARACTERISTICS AND RESPONSE TO TREATMENT

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Rationale: Patients with Refractory Status Epilepticus (RSE) present high morbidity and mortality. Few pediatric series have been reported. We analyze the epidemiological, clinical, and electroencephalograpic features in pediatric patients with RSE.

Methods: Retrospective study including patients under 15 years of age, admitted to Catholic University Hospital between November 2005 and May 2010, who underwent continuous electroencephalograpic monitoring (cEEG). Patients were identified from the EEG laboratory records. RSE was defined as any clinical or electrical seizure (or both) lasting for more than 60 minutes and persisting after receiving first and second line antiepileptic drug (AEDs) treatment. Four line of treatments were defined: (1) benzodiazepines, (2) phenytoin, valproate and/or phenobarbital, (3) midazolam, propofol or thiopental infusion, (4) any other drug or ketogenic diet. Patient clinical information was collected by chart review and included age, sex, preexisting medical and neurological conditions, seizure history, types of anticonvulsants used, neuroimaging findings and outcome at the time of discharge from hospital.

Results: We identified 13 patients with RSE, 12 male, mean age of 49,6 months upon admission (range 1,5-156 months). 7 had prior diagnosis of epilepsy and were taking a mean of 4 AEDs. Brain magnetic resonance was normal in 6/13 on admission. In 2, the initial EEG showed electrical seizures, in 4 interictal discharges and 4 had diffuse slowing. After initiation of cEEG, 9 presented convulsive status epilepticus (SE) and 4 Nonconvulsive status epilepticus (NCSE). cEEG showed that five patients with SE evolved into NCSE. Subsequently, therapy was modified in 10 patients. 5 patients had an acute symptomatic cause, 4 had remote ethiologies, 3 progressive diseases and 1 was associated to fever. Regarding treatment, one patient responded to second line treatment, three to third line, seven to fourth line, one persisted on status and one died. RSE remited on average at 9,6 days (1-47) and cEEG extended for a mean of 12,4 days (3-49). Most frequent complications associated to treatment of SE and NCSE were respiratory depression and hemodynamic inestability. One patient had Propofol infusion syndrome. At discharge, 8 patients had difficult to treat epilepsy and neurological deficit, 3 had epilepsy, one returned to baseline and one died. All epileptic patients were receiving at least 3 AEDs.

Conclusions: The majority of our patients evolved with difficult to treat epilepsy and neurological deficits, confirming the high impact of this condition on the neurological development of affected children. There was a high incidence of NCSE after SE (55,5%). Although this is a small series, these findings coincide with previous reports. Although 10/13 initial EEG were abnormal, cEEG was more useful in the monitoring and treatment of these patients. This technique is scarcelly availaible in our country and its use should be encouraged to improve management of SE.

3.078

EFFECTS OF VAGAL NERVE STIMULATION ON PATIENTS WITH EPILEPSY AND MENTAL RETARDATION

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Rationale: Epilepsy occurs in about one-third of all people with severe intellectual disability and about one-sixth of those with mild intellectual disability.

The treatment of epilepsy syndromes (e.g. LGS, chromosomal disorder with epilepsy, brain malformations, epileptic encephalopathies…) remains difficult in this group of patients, freedom of seizures is rarely achieved. Polypharmacotherapy and side effects are frequent, sometimes surgical management is possible, callosotomy is a palliative surgical treatment of last choice. Therefore our study aimed to evaluate vagal nerve stimulation (VNS) as non-pharmacological and non-resective treatment-option in this group of patients.

Methods: We investigated prospectively 42 adult patients with epilepsy and mental retardation before and after implantation of VNS with respect to seizures (drop attacks, status epilepticus), psychiatric comorbidity (depression, interictal dysphoric disorder/IDD, psychosis) and quality of life.

Patients were monitored at least 6 months before implantation, follow up lasted at least 12 months (in- and outpatient based). Results were determined during the last 3 months of follow up.

Results: 26 patients (61%) responded with a reduction of total seizure frequency of more than 50% (10 patients / 23 %: >75%). 13 of 31 patients (42 %) had a reduction of severe drop attacks of more than 50%. The magnet could be used successfully for interrupting auras / series in 23 patients (42%).

7 of 12 patients (58%) had significant benefit with respect to depression /IDD. In patients with non-affective disorders (psychosis) no effects were seen. Significant side effects did not occur.

VNS was valued as very good in self-rating, by families and caregivers in 38 of 42 cases (90%).

Conclusions: Our results support the indication of VNS particularly in this group of patients. Effects are long lasting and worthwhile not only on seizures, but as well on comorbidity with affective disorders. Tolerability was good, side effects were easy to handle. VNS can considerably improve the quality of life.

3.079

LACOSAMIDE AS ADD-ON THERAPY IN PEDIATRIC EPILEPSY: RETROSPECTIVE CLINICAL EXPERIENCE

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Rationale: Many children with intractable epilepsy require rational polytherapy. ideal drugs offer broad spectrum and minimal side effects. Lacosamide represents a novel mechanism based on slow sodium channel modulation. This may offer safe add-on therapy for patients with intractable seizures in pediatric age group.Patients with intractable seizures under 17 years of age were offered lacosamide as add-on therapy. this represented an off label use based on current labeling for use in ages 17 and above. Rational polytherapy wiht novel mechanism may offer advantages over prior monotherapy, or older antiepileptic agents.

Methods: All patients under 17 years of age offered lacosamide add-on therapy between June 2009 and September 2009 had charts reviewed for efficacy, and side effects from lacosamide. Data for number of other drugs used with add-on, age, and duration of therapy were reviewed.

Results: Twenty-three patients received lacosamide under the age of 17 years. Average age was 7.25 years (range 1.75-16). Dosage averaged 100mg/day (average 3.6mg/kg) and seizure efficacy showed > 50% reduction in 10/23 patients(43%with1patient complete control, 2 patients > 80% improved). Adverse effect was dizziness, or fatigue in 2 patients only. Idiopathic partial seizures improved greater than patients with generalized epilepsy, or congenital brain malformations; two cases CSWS had no response.

Conclusions: Lacosamide is safe and well tolerated in patients with intractable epilepsy. Those with partial seizures of idiopathic non-lesional type had greatest response. No help was seen in 2 cases of CSWS. More controlled observation of lacosamide in pediatric epilepsy as add-on therapy is warranted.

3.080

PILOT FEASIBILITY TRIAL OF THE ACUTE AND LONG-TERM SAFETY OF EXTERNAL TRIGEMINAL NERVE STIMULATION FOR EPILEPSY

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Rationale: Trigeminal nerve stimulation (TNS) is an emerging therapy for drug resistant epilepsy. Establishing the safety of external TNS is essential to future phase II and phase III clinical trials. We report the safety and tolerability of external TNS from the initial pilot feasibility study, and the effect of external TNS on acute and long-term heart rate, systolic and diastolic blood pressure.

Methods: Research committee approval was obtained for a pilot open study of external TNS in epilepsy. Informed consent was obtained before enrollment. Inclusion/exclusion criteria were age 18-65 years, > 3 complex-partial/generalized tonic-clonic seizures/month, no progressive medical conditions, and exposure to > 2 antiepileptic drugs (AED's). Subjects were enrolled in a 4-week pretreatment baseline, and were evaluated at 1, 2, 3, 6, and 12 months. AED's remained unchanged unless essential for patient safety. Stimulation settings were as follows: frequency 120 Hz, pulse duration 250 us, < 30 seconds on and < 30 seconds off for 12 - 24 hours per day. 1.25-inch disposable, silver-gel, adhesive electrodes were utilized, spaced 2 inches apart. Initially, unilateral infraorbital stimulation was utilized in subjects 1-3, but subsequent subjects have undergone bilateral supraorbital stimulation. Serial blood pressure and heart rate monitoring was performed every 5 minutes for one-hour on the first day of stimulation. Routine pulse, blood pressure, and clinical examinations were performed at each subsequent visit.

Results: 13 subjects were enrolled. TNS was well tolerated. Side effects included skin irritation in five subjects, which improved by reducing stimulation to 12-16 hours/day, or with hydrocortisone 1% cream. Tingling, forehead pressure, and headache were reported, but

improved with reduction of current. On day one of treatment, the mean pre-treatment heart rate (bpm) was 70.6 SD 11.2, versus 67 SD 10.3 after one hour of stimulation (n/s, $p > 0.05$) Pretreatment mean systolic blood pressure (mmHg) was 125.7 SD 13.4, versus 123.7 SD 15.1 after one hour of stimulation (n/s, $p > 0.05$ t-test). Likewise, pretreatment diastolic blood pressure (mmHg) was 70.5 SD 8.7, versus 70.2 SD 10.4 after one hour of stimulation (n/s $P > 0.05$). Long-term heart rate, systolic and diastolic blood pressure were not significantly changed at six months compared with the pretreatment baseline (all comparisons n/s, t-test, $p > 0.05$).

Conclusions: External TNS was well tolerated. Skin irritation was the most common side effect. External TNS was not associated with acute or long-term effects on heart rate, systolic or diastolic blood pressure. This pilot study provides evidence of excellent acute and long-term safety of external TNS for epilepsy. This study provides the foundation for larger double-blind safety and efficacy trials.

3.081

MEDICAL SIMULATION OF SENTINEL EVENTS: VALIDATION AND IMPLEMENTATION OF A TEAM TRAINING CURRICULUM FOR PATIENT SAFETY IN THE EPILEPSY MONITORING UNIT (EMU)

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Rationale: Patient safety has emerged as a critical topic for directors of EMUs. Assessment and management of changes in patient condition in the EMU is a complex process involving multiple providers with varying levels of training and experience. Successful management requires effective communications, hand offs, and the institution of a variety of therapeutic strategies. These factors increase delay in treatment and errors in care, potentially leading to adverse events. Although such events are uncommon, they have been reported in the EMU. To address these complexities and support effective team performance, we developed a simulation-based team training program for nurses and physicians to maximize their ability for safe care in the EMU. Medical simulation is an effective method of training medical teams, improving assessment, decision-making, and the institution of treatment strategies in unanticipated patient events. Using simulated scenarios based on actual EMU sentinel events, we aimed to introduce and educate neurology residents and nurses to the essential procedural and decision making steps required for EMU care.

Methods: We used a mixed methods study design for two distinct phases of this research project: expert review and consensus in appropriate patient management, and creation and implementation of a simulation based curriculum for multidisciplinary teams. The initial needs assessment/"gap analysis" used prior EMU sentinel events as well as the results of hospital root cause analyses (RCAs). A local panel of experts, including two nurses, and three neurologists all with >5 years experience in the EMU and one emergency physician, reviewed the videos of sentinel events and RCAs to identify critical procedural and decision making steps necessary for maximizing care. Through an iterative process to obtain expert consensus, a 14 item procedural checklist was developed to deconstruct and assess appropriate patient care performance. Once the checklist was developed and validated through expert review, the simulation curriculum was initiated. Consent to videotape and review simulations was obtained from participants and the study was approved by the IRB. After receiving an introduction emphasizing teamwork, leadership, communication, and evaluation of change in patient condition in the EMU, subjects were introduced to the medical simulator. Employing the procedural checklist and through interactive video-debriefing, trained facilitators identified strengths and weaknesses of individual and team performance and emphasized essential objectives.

Results: A simulation-based team training curriculum and procedural checklist was created and validated for patient safety in the EMU using review of sentinel events and RCAs.

Conclusions: A practical simulated curriculum is feasible and valid to train seizure safety in the EMU and may have broader applications for safety training. Reliability of the procedural checklist is planned by measuring kappa coefficients for inter-rater agreement of the assessed simulations.

3.082

SELECTIVE SEROTONIN REUPTAKE INHIBITORS: A SAFE TREATMENT FOR DEPRESSION IN CHILDREN WITH REFRACTORY EPILEPSY

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Rationale: Treatment for depression in children with epilepsy is often neglected, partly because of concerns related to the use of antidepressive drugs, especially in patients with refractory epilepsy. The aims of the following study were: to evaluate the safety and efficacy of the use of selective serotonin reuptake inhibitors (SSRI) in the treatment of depressive symptoms in children and adolescents with epilepsy.

Methods: A retrospective study was carried out by revision of a database and systematic analysis of medical records of 53 children and adolescents with a diagnosis of epilepsy and depression. We excluded from the study patients with other psychiatric disorders, with poor treatment adherence and those with problems in quantifying frequency of epileptic seizures. Worsening of seizure frequency was related to use of SSRI when occurring in up to three months after either its introduction or titration. We evaluated the effectiveness of SSRI treatment according to psychiatric assessments of the patient and judgments made by close family members.

Results: Out of 53 children and adolescents included in the study 69,8% either presented incomplete seizure control or were on antiepileptic drug (AED) polytherapy. Seizure frequency worsening occurred in 2 patients (3.8%), one of which seizure remission was obtained after increase in AED dosage. Improvement of depressive symptoms with SSRI use was observed in 96% of all patients (52/53) and a total remission of depression in 62,3% (33/53).Adverse effects occurred in 09 patients (17%), of which some with more than one adverse effect. Adverse effects were: skin rash in 3,8%, gastrointestinal discomfort in 3,8%, weight loss in 3,8%, drowsiness in 3,8%, nocturnal enuresis in 1,9%, hematological disorders in 1,9%, and irritability in 1,9%. Treatment was discontinued in 12 patients due to adverse effects (11, 3%), partial or total inefficacy (7.5%), poor treatment adherence (1.9%) and worsening of epileptic seizures (1.9%). In seven out of these patients, the change for other SSRI lead to remission of adverse-effects or efficacy improvement.

Conclusions: In our group of children and adolescents with epilepsy and depression, SSRI were considered as a satisfactory therapeutic option, when considering its efficacy in the remission of depressive

symptoms, relatively few adverse effects and very rarely seizure worsening. Therefore, when taking into account the greater incidence of symptomatic epilepsy in children, with frequent seizures, when compared to the adult population, SSRI may be considered as a safe and effective therapeutic option.

3.083

CONTINUOUS MIDAZOLAM INFUSION USE IN THE CESSATION OF NEONATAL STATUS EPILEPTICUS WHILE ON CONTINUOUS VIDEO EEG MONITORING

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Rationale: Neonatal status epilepticus (NSE) is frequently encountered in the neonatal intensive care unit, most often as the result of acute brain injury or infection. It is believed that electrographic cessation of seizures, rather than clinical resolution, is vital to improving outcome in these infants. The first-line treatment of phenobarbital has a 50% efficacy, which only slightly improves with the addition of the traditional second-line phenytoin. There has been growing interest in the use of midazolam in neonates, with recent literature illustrating variable results. Our objective is to characterize the electrographic response of NSE to continuous midazolam infusion, with specific attention to efficacy, rate of response and adverse effects.

Methods: All high risk infants with clinical seizure or moderate-to-severe hypoxic-ischemic injury were monitored on continuous video EEG. All infants received an initial loading dose of phenobarbital, repeated up to total of 30-60 mg/kg. Patients identified as being in NSE despite phenobarbital received IV midazolam bolus (0.1 mg/kg), while continuing on EEG monitoring. If seizures persisted, midazolam was administered by continuous infusion (0.1 mg/kg/hr), and titrated as necessary.

Results: Six patients were identified in a 3 month time period as being in NSE despite loading doses of phenobarbital. Seizures started between 0 hours of life and 10 days of life, and were due to various etiologies (see table 1). The midazolam was started within 24 hours of seizure identification in 5 of the 6 patients. Status epilepticus (SE) stopped with initiation of versed in all patients. Electrographic seizures stopped after versed bolus in 1 patient, within several minutes after initiation of midazolam drip in 2 patients, within hours in 2 patients, and decreased dramatically in 1 patient who was subsequently withdrawn for septic shock due to complete bowel infarction. All 5 surviving newborns remained seizure-free on phenobarbital alone after removal of versed drip. There were no notable clinical side effects from the midazolam infusion.

Conclusions: Midazolam infusion should be considered an option in the management of NSE. It works rapidly to control status epilepticus, often resulting in complete cessation of seizures, even in those patients who had been refractory to high levels of phenobarbital. More attention and significant work needs to be done to provide better age appropriate options of SE in the NICU population.

Table 1. Summary of Patient Etiology and Seizure Response

IMAGE: tables/906512_T1.jpg

* Pt in status epilepticus when placed on video EEG. No clinical seizure. Unknown onset.

** Support was withdrawn due to multi-system organ failure, shock and necrotic bowel

***Seizures reported in the delivery room, exact time unknown

Phenobarbital given in boluses of 10-20 mg/kg

^Pt had seizures initially controlled by phenobarbital, then returned and evolved into NSE requiring the midazolam

HIE = hypoxic ischemic encephalopathy

3.084

PREDICTORS FOR SEIZURE OUTCOME IN A PROSPECTIVE AVM DATABASE USING MULTIMODAL TREATMENT STRATEGIES

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Rationale: Brain AVM patients experience seizures in 20 to 30% of cases. 1 out of 100 unprovoked first seizures is caused by AVMs. AVMs are considered to be models for epileptogenic lesions as a result of perilesional gliosis, hemorraghe, steal phenomena, and iron deposits. The aim of this study was to define predictors for seizure outcome in a large prospective data base with specific focus on the role of intervention.

Methods: Between 1982 and 2007, the University of Toronto Brain AVM Study Group treated 1106 patients with brain AVMs, of which 333 (30.1%) experienced seizures (SZ-Group). 155 patients met inclusion criteria for this study including a complete set of clinical and neuroradiological data. Mean (±SD) follow up was 7.35±5.43 years. Treatment consisted of surgical resection, radiosurgery or embolization, either alone or in combination. A total of 49 variables were examined; outcome was determined by Engel seizure outcome scale. These data were compared for statistical relevance to 50 AVM patients with no seizures (Non-SZ-group) over the course of the disease. Mean follow-up was 5.04±4.8 years.

Results: The SZ-group was diagnosed with AVM at age 35±13 years compared to the Non-Sz-group with age 39±18 years. Infratentorial, occipital and deep white matter location were found in 46.0% in the Non-Sz-group versus 8.5% in the Sz-Group ($P<0.01$). Small sized AVMs occured in 68.1% of the Non-Sz-group vs. 43.8% in the Sz-group ($p<0.01$). The number of treatment procedures was significantly higher in Sz-group ($P=0.01$). 58.1% of the Sz-group became seizure free, and 30.0% stayed seizure-free after weaning off antiepileptic drugs (AED). Predictors for a good seizure outcome were generalized tonic-clonic seizures ($P<0.01$), intervention after single sz ($P<0.01$), and complete obliteration of the AVM ($P<0.01$). The Non-Sz group presented significantly more often with bleeding events ($P<0.01$). Factors significantly reducing chance of a favorable outcome ($P<0.01$) were focal seizures, particularly complex-partial seizures, transition from GTCS to CPS or SPS, and embolization in single modality treatment.

Conclusions: Our data strongly suggest that an early diagnosis of AVM after single sz presentation and a subsequent rigorous treatment approach (leading to complete obliteration of the AVM) leads to the overall best seizure outcome. We speculate that delayed diagnosis may lead to secondary epileptogenesis and unfavourable seizure outcome.

3.085

THE EFFECTS OF INTRACRANIALLY-PLACED ELECTRODES FOR EPILEPSY SURGERY IN SEIZURE FREQUENCY

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Rationale: Introduction

It has been our observation that in most cases admitted to the epilepsy monitoring unit (EMU), seizure frequency reduces when patients undergo intracranial placement of electrodes for epilepsy surgery evaluation.

Methods: Methods

Patients with medically-intractable epilepsy admitted to the EMU, between April 2008 and March 2010, were included in the study. Their seizure frequency during scalp video-EEG evaluation was compared with that seen during video-EEG with intracranially-placed electrodes. Patients with status epilepticus were excluded. Demographic and clinical variables, location of epileptogenic focus, number of electrodes, length of stay, number of lobes recorded, and presence of complications, were taken into account.

Results: Results

50 patients (25 female), with a mean age of 35.8 (range: 17-59), were included. Most were non-lesional (41 had normal MRI). All patients had subdurally-implanted strips, 2 had additional grid, and one patient additional depth electrodes. Mean number of electrodes was 96 (+/- 43). Seventeen had unilateral coverage and 33 bilateral, with an average of 3 lobes covered. 61% had an epileptogenic focus in the temporal lobe(s) (25% right, 29% left, 7% bilateral), 25& frontal, 5% occipital, 5% parietal, and 4% had multifocal epilepsy. Average length of stay was 15 days (+/- 9.4). Seizure frequency was 7% less with intracranial electrodes as compared with scalp video-EEG ($p<0.05$).

Conclusions: Conclusion

The benefit of intracranially-placed electrodes in localizing the epileptogenic focus is clear, but the finding that they may decrease seizure frequency, indicates the need of prolonged recordings.

3.086

PROPOFOL INFUSION SYNDROME IN PATIENTS WITH INTRACTABLE STATUS EPILEPTICUS

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Rationale: The propofol infusion syndrome (PRIS) is known to be found in status epilepticus (SE) patient treated with propofol. PRIS is defined as a syndrome which has more than one feature such as metabolic acidosis, cardiac dysfunction, rhabdomyolysis, lipidemia, hepatic dysfunction, death, arrhythmia, or renal dysfunction. But there is still controversy whether PRIS is caused by propofol itself or by status epileptics per se. Our aim is to investigate whether propofol treatment may change the course of SE and cause the features of PRIS in SE.

Methods: We enrolled 32 patients who were diagnosed as SE from Jan 2005 to Jan 2009. After dividing them into SE group with propofol (SE+, N=13) and SE without propofol (SE-, N=19) we analyzed and compared the demographic factors, previous medical history, seizure semiology, etiology of SE, the kinds and dosage of antiepileptic drug, duration of hospital stay, neurologic status at discharge, and clinical components of PRIS between two groups.

Results: In SE+ group (mean age 29.9± 13.4 yrs), mean dosage of propofol was 77.2 + 63.3 mg as bolus, mean infusion rate was 4.9 + 3.0 mg/kg/hr, and the peak infusion rate was 7.3 + 4.8 mg/kg/hr. Mean duration of propofol infusion was 153.3 + 151.6 hours. Among them, 12 patients (92%) could be diagnosed as PRIS: hypotension was found in 12, dyslipidemia in 3, and metabolic acidosis in 4, cardiac dysfunction in 4, rhabdomyolysis in 6, hepatic dysfunction in 6, death in 5, cardiac arrhythmia in 5, and renal dysfunction in 3 patients. However, there was no significant difference in the frequency of acidosis, cardiac dysfunction, rhabdomyolysis, hepatic dysfunction, dyslipidemia, death, arrhythmia, and renal dysfunction, the duration of hospital days, and the seizure outcome between SE+ and SE-. The incidence of hypotension or dyslipidemia was definitely higher in SE+ group, but that did not influence on the overall prognosis of SE.

Conclusions: Propofol treatment frequently caused hypotension and dyslipidemia in patients with SE, which were components of PRIS. However, the incidence of PRIS was not related to propofol dosage/ infusion rate but to SE itself. Our findings suggest that the presence of PRIS did not influence of the prognosis of SE.

3.087

SELENIUM STATUS OF CHILDREN TREATED WITH THE CLASSIC AND MEDIUM-CHAIN TRIGLYCERIDE (MCT) KETOGENIC DIETS

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Rationale: The ketogenic diet is an effective therapy for intractable epilepsy, despite documented associated adverse effects. Among the reported nutritional deficiencies in children treated with ketogenic diets, selenium deficiency has been described, associated with cardiomyopathy and one case of sudden death. The objective of this study is to assess the selenium status of children treated with the classic and MCT ketogenic diets in two facilities in Toronto, Canada.

Methods: Fifty children, age 0.5-12.5 years (mean±SD=5.07±3.27), were treated with a ketogenic diet from March 2003 to March, 2010. Twenty-three children, 14 boys, (age: mean± SD=4.35±3.33) were treated with the classic diet and 27 children, 17 boys, (age: mean±SD=5.61±3.21) were treated with the MCT ketogenic diet. Plasma selenium levels were collected pre-diet, and at 6 months and 12 months during diet treatment. The laboratory selenium reference range used was 1.27-2.09 umol/L. Selenium supplementation was prescribed at diet initiation if total intake did not meet the Dietary Reference Intake (DRI). Supplementation was adjusted for individual children if a single selenium level fell below the reference range on routine bi-annual testing. T-tests were performed to compare selenium levels of children treated with the MCT and Classic diets at diet initiation, and at 6 and 12 months on diet therapy. Paired t-tests were used to compare pre-diet and 6 and 12 month selenium values in each diet group.

Results: Prior to diet initiation, there were 9 children in the classic diet group and 3 children in the MCT diet group with selenium levels below the recommended range. In 23 children treated with the classic ketogenic diet, mean plasma selenium prior to diet initiation was 1.37±0.34umol/L, increased to 1.66±0.61umol/L at 6 months and 1.60±0.41umol/L at 12 months. Levels were significantly higher during diet therapy ($p<0.05$).

In 27 children treated with the MCT ketogenic diet, the mean±SD plasma selenium prior to diet initiation was 1.55±0.34umol/L, remaining quite stable at 6 months, 1.57±0.35umol/L, and 12 months, 1.57±0.32umol/L. There was no significant difference between pre-diet and during diet levels in this group.

There was no significant difference between the mean selenium levels in children treated with the MCT compared to the classic ketogenic diet at any time point.

Conclusions: Selenium deficiency has been associated with cardiomyopathy. Ketogenic diets are nutritionally deficient and place children with intractable epilepsy at risk of selenium deficiency. In this group, 12 of 50 children had selenium levels below the recommended range prior to initiation of a ketogenic diet. However, with careful monitoring and supplementation, all children in this cohort maintained adequate selenium levels during diet treatment.

3.088

USE OF NUTRITIONAL SUPPLEMENTS AND RECREATIONAL SUBSTANCES IN ADULTS WITH EPILEPSY IN TERTIARY CARE

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Rationale: Use of recreational substances may affect seizure control and well being in people with epilepsy. Similarly, regular nutritional supplementation is important, especially when using enzyme inducing AEDs and in women of childbearing age. We examined these aspects in adults referred to a tertiary care epilepsy program.

Methods: The University of Calgary Division of Neurology is the main tertiary referral centre for adults with epilepsy, serving 1.3 million people. We prospectively captured data on consecutive adults with the diagnosis of epilepsy at the 1st encounter in our outpatient epilepsy program, using a validated data capture and verification system, excluding patients with single seizures and children. We captured information on regular usage of alcohol, recreational (illicit) drugs, and tobacco, and on regular supplementation with folic acid, multivitamins, calcium and Vitamin D. We tabulated data and analyzed the association of use with pertinent clinical variables using chi-square statistics.

Results: In 687 consecutive patients (52% women) the mean age and duration of epilepsy was 40 and 12 years respectively, 64.1% had focal epilepsy, 23% had idiopathic generalized epilepsy, and 21% were seizure free in the past year. Forty percent of patients regularly consumed alcohol (males 44%, females 36%, p=0.03), 26% smoked tobacco (males 32%, females 20%, p=0.001), and 12% used recreational drugs (males 11%, females 9%, p=ns). Seizure free and non-seizure free patients did not differ in their use of alcohol (41% vs 40%) and recreational drugs (7% vs 11%), but fewer seizure free patients smoked tobacco (17% vs 28%, p=0.03). There was no difference in use of alcohol in those with focal (38%) or generalized (40%) seizures. But fewer patients with focal seizures used recreational drugs (7% vs 12%, P=0.08) or smoked tobacco (21% vs 30%, p=0.03). There was no difference in the rate of use of these three substances between the group overall and those with self-reported anxiety or depression. More women than men used regular supplements of multivitamins (39% vs 32%, p=0.08), folic acid (10% vs 5%, p=0.01), calcium (29% vs 16%, p<0.001), and Vitamin D (30% vs 19%, p=0.001). Of 9 pregnant women only 3 were on folic acid. Seizure free and non-seizure free patients did not differ in their use of multivitamins (41% vs 33%), folic acid (7% vs 8%), calcium (27% vs 21%), and Vitamin D (28% vs 23%).

Conclusions: Overall use of recreational substances was similar to that of the general population, but males were heavier users than females. Substances were used equally by patients who were and were not seizure free, raising the question of their role as seizure triggers. Fewer patients with focal seizures used substances, an observation requiring further exploration. Women were more likely to use nutritional supplements, but less than a third used calcium and Vitamin D, and only one third of pregnant women were on folic acid. Efforts need to be devoted to improving these health related behaviors in patients with epilepsy.

3.089

INTRAOPERATIVE ELECTROCORTICOGRAPHY IN TEMPORAL LOBE EPILEPSY SURGERY

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Rationale: To determine whether intraoperative electrocorticography (ECoG) can aid in tailoring the extent of resection in temporal lobe epilepsy (TLE) and predict outcome. We investigated an association between intraoperative ECoG findings and seizure outcome in a series of TLE patients.

Methods: Consecutive patients who underwent temporal lobe surgery between 1993 and 2009 were included. Patient demographics including date of surgery, seizure localization, duration of epilepsy, and results of pre-operative surgery evaluation including ECoG data were analyzed. Surgical outcome, pathology, and Engel criteria were obtained. For patients who underwent a second operation for epilepsy (N=2), ECoG data from the first operation was used. Recorded spikes were classified based on frequency of occurrence as occasional, frequent, very frequent and ictal patterns.

Results: One-hundred-and-seven temporal lobe resections were performed on 99 unique patients. Of these, 56 patients (57%) underwent intraoperative ECoG recordings at the time of surgery, immediately prior to and after resection, without any other prolonged intracranial recordings. Temporal lobectomy was performed in 42 of those patients, 14 underwent lesionectomy. Thirty-five patients were male (62%). The mean age at surgery was 40 years (yrs) (range= 23-82 yrs), and the average duration of epilepsy was 24 yrs (range =2-51 yrs). Thirty-four (61%) of the surgeries involved the left temporal lobe. The average follow-up period was 5 yrs (range: 6 months-17 years). Neuropathology revealed mesial temporal sclerosis in 32% (18 patients), mild gliosis (21), neoplasia (11), heterotopia (2), vascular malformation (1), and normal appearing tissue (3). ECoG was performed with intraoperative subdural electrodes using an 8-contact strip in 77% of cases, the remaining involved various configurations of

grids and strips. Pre-resection recording from 1 or 2 locations was accomplished in 64% of cases, while recording from >2 locations occurred in 36%. Epileptic discharges were detected in 89% of pre-resection recordings, with 62% occurring in the inferomedial temporal lobe. Spike frequency was categorized as occasional (58%), frequent (38%), or very frequent (2%). Ictal patterns were also identified (2%). After the initial resection, spikes were still identified in 54% of cases (n=30). Of those, 63% (n=19) went on to have further resection. On follow up after an average of 5 yrs, Engel class I was achieved in 23 out of the 26 patients who were spike-negative after their initial resection (88%), and in 19 patients out of the 30 patients (63%) who continued to have spikes after the initial resection ($p < 0.05$).

Conclusions: Intraoperative ECoG in TLE surgery predicts outcome. Lack of intraoperative ECoG spikes after temporal lobe resection lead to improved outcome. While ECoG is not routinely performed in temporal lobe surgeries for epilepsy, our data suggests that ECoG may help predict outcome, with the absence of post-resection spikes linked to Engel I scores. Prospective studies to validate this observation are needed.

3.090

EFFECT OF SEIZURES ON COGNITION, BEHAVIOR, AND QUALITY OF LIFE DURING CARBAMAZEPINE OR LAMOTRIGINE MONOTHERAPY IN PATIENTS WITH NEWLY DIAGNOSED PARTIAL EPILEPSY

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Rationale: Previous studies suggested that patients with epilepsy tend to have poorer cognitive function, personal or social behavior and quality of life (QOL) than normal subjects. But there are limited data presented how much recurrent seizures have influence on cognition, behavior, and quality of life in newly diagnosed epilepsy. We investigated seizure effect to cognitive function, behavioral changes, and quality of life during 48 weeks treatment with lamotrigine (LTG) or carbamazepine (CBZ) monotherapy in patients with newly diagnosed or untreated partial epilepsy.

Methods: Newly diagnosed and untreated partial epilepsy patients randomized to receive LTG or CBZ monotherapy. Study duration consisted of 8-week dose titration period and 40-week maintenance period. Patients categorized in seizure-free or not-seizure-free subgroup during 40-week maintenance period. Neuropsychological test, symptom check list-90, and QOLIE-31 assessed at baseline, 16 weeks and final 48 weeks. Primary outcome measured by group-by-time interaction to evaluate seizure effect between subgroups at baseline and 48-week endpoint. Secondary outcome measured by changes of cognitive and QOL scores to seizure effect between subgroups. Linear-mixed model analysis applied to estimate time-variable change of scores combined with seizure effect.

Results: A total of 110 patients were eligible and 73 completed the 48-week study (LTG, n=39, 68.4%; CBZ, n=34, 64.2%). Our primary outcome revealed with group-by-time interaction in two subscales of California Verbal Learning Test (CVLT) [serial clustering index ($p<0.001$) and recognition ($p=0.020$)], overall QOL score ($p=0.020$) and two subscales of QOLIE [seizure worry ($p<0.001$), social score ($p<0.001$)]. Seizure effect became more significant in performance with serial clustering, and narrowed differences between subgroups in performance with recognition of CVLT.

Seizure-free group revealed significant improvement of overall QOL score, seizure worry and social score in about of group-by-time interaction.

Secondary outcome showed intergroup differences measured by Rey Complex Figure Test (RCFT) copy ($p=0.035$), correct response of Stroop color ($p=0.029$), Stroop Word/Color Interference Task ($p<0.001$), two subscales of Controlled Oral Word Association Task (COWAT) [semantic fluency task ($p<0.001$), phonemic fluency task ($p=0.042$)], three subscales of CVLT [short delay free recall ($p=0.017$), long delay free recall ($p=0.026$), long delay cued recall ($p=0.023$)], and one subscale of QOLIE (energy, $p=0.021$) with better performance in seizure-free group.

Conclusions: Our results suggested that recurrent seizures have some negative influences on cognitive function and QOL. Seizure free significantly improve overall QOL, but there is no significant effect in behavior. Difference between treatment with LTG and CBZ were not significant, needed more direct comparing study.

3.091

FACTORS CONTRIBUTING TO DRIVING IN PATIENTS WITH EPILEPSY IN KOREA

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Rationale: People with epilepsy are generally restricted from driving because of the concern over seizure-related motor vehicle accidents while driving. There are only few studies concerning factors associated with poor compliance with driving regulations in patients with epilepsy. We investigated the characteristics associated with driving in people with epilepsy and aimed to identify factors associated with driving in those patients with uncontrolled seizures.

Methods: Survey was conducted to patients being treated for epilepsy in four university hospitals in Korea. Men and women were recruited with a ratio of approximately 2:1 because men are more likely to drive than women in Korea. Questions were asked by a doctor to each patient attending outpatient clinic. The interview was designed to collect their socio-demographic data and epilepsy-related data (age at seizure onset, seizure duration, seizure types and frequency, number of antiepileptic drugs taken). There were also driving related questions (possession of driving license, driving status during the last year, driving frequency, driving hours/day, cause of driving, any experience of accident).

Results: Of 290 patients with epilepsy interviewed, 58% had a driver's license and 40% had driven during the last year. Among those with uncontrolled seizures, 54% reported to held a driving license and 36% had driven a car in the past year. Five percent of the total participants reported having experienced at least one or more seizure-related accidents while driving, and it was more reported by those with

uncontrolled seizures compared to those with controlled seizure (7.3% vs 1.8%, p = 0.02).

In a multivariable analysis, being male (OR = 0.289, p = 0.02), being married (OR = 4.325, p = 0.002), being employed (OR = 3.328, p = 0.005), and taking fewer antiepileptic drugs (OR = 3.328, p = 0.05) were the four factors associated with increased likelihood of driving in patients with uncontrolled seizures.

Conclusions: Our study demonstrated that a significant number of people with uncontrolled seizures, those who should not be driving, continue to drive and that being male, married, employed, and taking few antiepileptic drugs were the major reasons for these individuals to continue to do so.

3.092

LACOSAMIDE IN THE TREATMENT OF ACUTE RECURRENT SEIZURES AND PERIODIC EPILEPTIFORM ACTIVITY IN CRITICALLY ILL PATIENTS

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Rationale: Lacosamide (LAC) is a novel adjunctive agent for partial seizures available in the U.S. since June 2009. The medication appears to be an ideal anti-epileptic drug (AED) for use in critically ill patients given its availability in dose equivalent oral and intravenous (IV) formulations, lack of hepatic cytochrome P450 isoenzyme induction, and minimal drug-drug interaction. We report our initial experience with LAC in critically ill patients with acute recurrent seizures or periodic epileptiform activity.

Methods: Using an EEG report database, we identified subjects who received LAC, PHT, or VPA while undergoing non-elective inpatient continuous EEG monitoring for recurrent seizures or periodic epileptiform patterns refractory to at least one AED between January 2007 and June 2010. Levetiracetam (LEV) was not included because of its frequency of use as a first line agent. Patient demographics, prior seizure history, underlying etiology, admission AEDs, AED changes, LAC titration schedule, adverse effects, and electrographic/clinical outcome were recorded. P-R intervals were measured on the single-lead EKG prior to and after starting LAC.

Results: A total of 17 patients received LAC as add-on therapy for acute recurrent seizures or periodic epileptiform activity. LAC was the second or third agent in 15 patients and the fourth or fifth agent in 2 patients. In 12 patients, introduction of LAC resulted in improvement of seizures or periodic epileptiform activity (70.6%). Two patients required additional agents to control seizures. There were no complications directly attributable to LAC, and LAC was not discontinued in any patient during hospitalization because of side effects. Two patients tolerated an initial dose of 300 mg IV LAC followed by 200 mg bid, and three other patients were started on 200 mg bid, 2 of whom received the drug IV without reported complications. The average P-R interval did not significantly change after introduction of LAC (p=0.41). Eleven of 17 patients were discharged with LAC, including 6 patients directly home. In 5 patients, medical care was withdrawn.

In comparison, 6 of 9 patients (66.7%) responded to PHT and 4 of 13 patients (30.8%) responded to VPA with EEG improvement. This suggests that the response rate to LAC is comparable to that of PHT and may be higher than that of VPA in our patient group. In addition, as a proxy measure of the effectiveness of LAC compared to LEV, 16 of 17 patients in our study were given LEV prior to LAC. Eleven of these patients had seizure improvement with initiation of LAC. Therefore, 64.7% of patients in our study were LEV-refractory and responsive to the addition of LAC.

Conclusions: Our data suggest that LAC is safe, well-tolerated, and effective as an add-on treatment in critically ill patients with acute recurrent seizures or periodic epileptiform activity refractory to at least one other AED. Its efficacy is at least comparable to other AEDs traditionally used in these patients.

3.093

CALLOSOTOMIES IN SWEDEN 1990-2004: DATA FROM THE THE SWEDISH NATIONAL EPILEPSY SURGERY REGISTER

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Rationale: Callosotomies have been used mainly in children with drop-attacks in intractable epilepsy. The procedure has been used less frequently since the vagus nerve stimulator was introduced for the same indication. Callosotomy has however got some revival. We present data on callosotomy in the Swedish epilepsy surgery program 1990-2004.

Methods: The Swedish National Epilepsy Register has national coverage and encompasses data on all patients operated in Sweden since 1990. For the purpose of the present study we analysed data from the period 1990-2004 regarding all callosotomy procedures. Seizure outcome is reported, even if the procedure is mainly palliative to prevent drop attacks and is also sometimes used to protect a healthier hemisphere in staging procedures such as early stages of Rasmussen encephalitis. Our definition of complications is that a minor complication is fully resolved d" 3 months, while a major complication persists and to some extent affects daily life.

Results: In all 85 callosotomies were performed, 68 anterior, 5 posterior and 12 complete. In 14 cases it was performed as a reoperation. Onset age of epilepsy was (mean; median, Q1; Q3) 3.7; 2.0; 0.4; 5.0 and age at surgery was 16.6; 14.0; 5.2; 23.3. In 42% the imaging was normal or inconclusive. IQ level was e"70 in 7.1%, 50-69 in 40.0% and below 50 in 52.9 %. Preoperative monthly seizure frequency was 396; 150; 50; 360. Four patients (4.7%) had undergone invasive evaluation. Postoperative seizure frequency was 169; 50; 3; 106. Of the patients with a completed 2-year follow up four patients became seizure free (5.4 %), 9 (12.2%) had more than 75 % reduction of seizure frequency, 16 (21.6 %) had 50-75% reduction of seizure frequency and 45 (60.8%) less than 50 % reduction. The four patients who became seizure free had a preoperative seizure frequency of 78; 31; 2; 107, which is almost half of what the remaining patients had. The number of callosotomies performed was 55 in1990-94, 23 in1995-99 and 7 in 2000-04. In the complete patient material the number of surgical complications were 5 (5.8%) minor (4 wound infections and one pulmonary embolism) and 1 (1.2%) major (a subdural hematoma resulting in a slight hemiparesis and mutism).

Conclusions: In spite of decreasing use, corpus callosotomy can be of certain benefit for selected patients, and may lead to a substantial reduction of seizure frequency. Even if seizure freedom is not the primary goal some patients do become seizure free and in this material 29 patients (39.2%) had a seizure reduction of more than 50%. Callosotomy should be considered when there is no focality, MRI

negativity, bilateral synchrony in the EEG and frequent drop attacks. In this material callosotomy was a safe procedure, with a low risk for complications. In Sweden there is a consensus to try vagus nerve stimulation first, and to consider callosotomy if the effect of VNS is insufficient.

3.094

SIMILAR RESPONSE TO ANTIEPILEPTIC MEDICATIONS AMONG EPILEPTIC SIBLINGS

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Rationale: When epilepsy does not respond to the initial antiepileptic drug (AED), the subsequent search for an effective AED is predominantly a matter of trial and error. Guidance to help predict efficacy of a particular AED is needed. We hypothesized that in familial epilepsy, affected family members share a common pathophysiology, and the identification of an effective AED in one member may be useful for the treatment of other affected members. We tested this hypothesis in siblings treated in our practice for epilepsy.

Methods: In a thorough search of our clinic database, we identified 13 siblings from six affected families, all of whom were treated in our clinic. All patients were studied with EEG or EEG-video monitoring and had their seizure and epilepsy classification verified. We recorded prior AED therapy in each sibling and the eventual AED or AED combination that produced seizure control.

Results: The patients were 5 women and 8 men, aged 23 to 44 years. The age at epilepsy onset varied from 4 to 29 years. Two of the families had generalized and four had partial epilepsy. All patients were drug-resistant at one point in their presentation. One set of siblings had recurrent episodes of status epilepticus. Five sets of siblings (11 individuals) became seizure-free or almost seizure-free (rare seizures related to compliance lapse or other precipitants in 4 individuals) with treatment modification. In these 5 families, the AED or AED combination that rendered one sibling seizure-free was used successfully in the other sibling(s). The medication that produced seizure freedom was lamotrigine in three families (including the siblings with recurrent status), lamotrigine-valproate combination in one family and lamotrigine-levetiracetam combination in the fifth family. In one remaining family with generalized epilepsy, one sibling was seizure-free on phenobarbital while the other had persistent seizures despite polytherapy.

Conclusions: Siblings with epilepsy tend to have a similar profile of AED response. The AED that proves effective for one sibling will likely be effective for the other, and thus may save un-necessary AED trials. Lamotrigine was the most commonly efficacious AED in the current group of siblings.

3.095

OUTCOME OF PATIENTS UNDERGOING HEMISPHERECTOMY FOR RASMUSSEN ENCEPHALITIS RECEIVING AN INTENSIVE POST SURGICAL REHABILITATION PROGRAMME

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Rationale: To determine the outcome of children with Rasmussen encephalitis (RE) treated with hemispherectomy and receiving a 12 week intensive inpatient rehabilitation programme.

Methods: Case note review with regard to pre-surgical status and outcome following a 12 week intensive inpatient rehabilitation programme and at last follow up.

Results: The case notes of seven children (4 male,3 female) were reviewed;median age at hemispherectomy 13 years (range 8.8-15.4 years). The median duration of seizures prior to surgery was 6 years (1.2-7.9 years). In all 7 cases pre-surgical assessments suggested language dominance in the left hemisphere. The dominant hemisphere was involved with RE in four cases. In three cases there was some evidence of re-organisation of language (neuropsychology and FMRI). Two cases required a further disconnection procedure for re-emergence of seizures (one developed hydrocephalus). Six were seizure free at last follow up. Following hemispherectomy there was improvement in: seizure control, antiepileptic drug load, mobility, activities of daily living and access to education. Comparing the status pre- and post-surgery and following rehabilitation there was most improvement in motor and self care skills. At follow up there was maintained improvement in seizure control and improvement in ambulation and in accessing education and school attendance.

Conclusions: Surgery improves seizure control in RE and longer term access to education. Children undergoing intensive post surgical rehabilitation benefit with regard to motor skills, ambulation and self care skills in the short term. Intensive post surgical rehabilitation is recommended as routine management for these patients with complex and multidimensional needs.

3.096

INTRAVENOUS LACOSAMIDE IN THE TREATMENT OF STATUS EPILEPTICUS

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Rationale: Lacosamide (LCM) is a newly approved antiepileptic medication (AED) with a novel anticonvulsant activity. The efficacy of LCM was reported in patients with partial epilepsy in pivotal trials, and the safety of intravenous LCM infusion (200-800 mg/day) over 10, 15 or 30 minutes was demonstrated in an open-label study. Its availability in intravenous solution, favorable pharmacokinetics, tolerability and lack of respiratory suppression make LCM as an attractive choice to treat patients in acute/critical settings. However, experiences of using LCM in these critical settings are quite limited. We reviewed the effectiveness of intravenous LCM in the treatment of status epilepticus (SE).

Methods: We retrospectively reviewed our inpatient hospital record to identify patients who had received intravenous LCM for status epilepticus between August 2009 and April 2010 at the Barrow Neurological Institute after obtaining IRB approval. Relevant clinical data including age, etiology of status epilepticus, AEDs administered prior to LCM and disposition were collected, in addition to EEG interpretations. Only the patients who had a diagnosis of SE by EEG criteria prior to receiving LCM were included in the study. All patients had continuous and /or routine EEGs prior to receiving intravenous LCM and during the first day after the first dose of LCM. Those patients who had been taking LCM prior to the diagnosis of SE were excluded from the study.

Results: We identified a total of 19 patients (12 males) who had received intravenous LCM for the treatment of refractory SE during this study period. Median age was 58 (ranged from 3 to 77) and only one patient was less than 18 years of age. Etiology of status epilepticus included vascular, neoplastic, infectious and anoxic causes. Prior to receiving LCM, patients were most frequently treated with lorazepam, fosphenytoin, and levetiracetam, followed by valproate, phenobarbital, carbamazepine, midazolam, diazepam, and propofol. The initial dose of LCM ranged from 50mg to 400mg followed by maintenance doses ranging from 100mg to 400mg per day. The pretreatment EEGs showed unilateral or bilateral periodic discharges in 7 patients, continuous or rhythmic epileptiform discharges in 10 patients, and burst-suppression patterns in 2 patients. 16 of the 19 patients (84.2%) had improvement in their EEG during the first day after receiving LCM, although12 of the 19 patients (63%) had recurrence of seizures during the hospitalization.

Conclusions: Our retrospective study suggests that intravenous LCM was effective in treating refractory SE. Coupled with its favorable pharmacokinetic profile and tolerability, LCM may be an useful alternative in the treatment of refractory SE. Further prospective study is needed to establish the definite efficacy of LCM in treating SE as well as its loading dose and infusion rate.

3.097

TO EVALUATE THE TOLERABILITY OF LACOSAMIDE AS ADD-ON THERAPY TO EITHER NON-SODIUM CHANNEL BLOCKING OR TRADITIONAL SODIUM CHANNEL BLOCKING ANTICONVULSANT AGENTS

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Rationale: Using lacosamide, a novel, non-traditional sodium channel blocking AED, as add-on therapy in patients with partial-onset epilepsy has resulted in various treatment-emergent adverse events. We undertook this study to evaluate the tolerability of lacosamide in patients that were concomitantly either on at least one traditional sodium channel blocking AED or on AEDs that act on non-sodium channel targets.

Methods: Retrospective chart review of 34 consecutive patients undergoing add-on therapy of lacosamide of up 400mg/day for intractable partial seizures. We collected data on concomitant AEDs classified as either non-sodium channel (NSCB) or sodium channel (SCB) blocking and compared number and character (e.g. dizziness, headache, nausea and vomiting, fatigue) of adverse events; necessary adjustments to concomitant AEDs or lacosamide; and number of discontinuations of lacosamide either due to intolerable adverse events or lack of efficacy between the two groups. Data were analyzed using Chi-square or t-test statistics, as appropriate.

Results: At baseline, eight patients were on AEDs acting on non-sodium channel targets (e.g. valproate, levetiracetam, topiramate, zonisamide, pregabalin, phenobarbiatal, clonazepam). Twenty-six patients were on traditional sodium channel blocking AEDs (e.g. carbamazepine, lamotrigine, oxcarbazepine, phenytoin). The two groups were not significantly different in age (NSCB=33.3 (+/-14.6); SCB=33.9 (+/-14.1), p=0.9) nor gender distribution (p=0.4). There were no significant group differences in the number or character of adverse events to lacosamide (both p's>0.2). Neither the need to adjust concomitant AEDs (p=0.7) nor the percentage in reduction required (p=0.8) varied for the two groups. There were no differences between the groups as to who had to discontinue lacosamide either because of side effects of increase in seizures (p=0.2).

Conclusions: Our study failed to show any difference in tolerability of lacosamide when added on to either a non-sodium channel blocking or traditional sodium channel blocking anticonvulsant agent. For our patients difficulties with tolerating lacosamide were not related to sodium channel classification of concomitant anticonvulsant medications. Indeed, patients on either type of concomitant medications experienced multiple adverse events. The reason for this difficulty with tolerability needs further evaluation.

3.098

POST HYPOTHERMIC STATUS EPILEPTICUS - IS IT TREATABLE?

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Rationale: Postanoxic status epilepticus is considered a poor prognostic sign. Hypothermic protocols have been implemented with some success. There is no consensus regarding management of postanoxic posthypothermic status epilepticus. It is important to know if treating these patients aggressively is beneficial. To this end we are reporting some results from our ongoing prospective observational study.

Methods: Five consecutive patients were included thus far from January 2009. They were treated for post-anoxic status epilepticus, if they had an anoxic event after cardiac arrest, underwent hypothermic protocol and had evidence of status epilepticus on EEG. Treatment included an initial loading dose of antiepileptic medication and if there was status epilepticus on continuous EEG, they were started on propofol (3-5 mg/kg IV bolus, 2-10mg/kg/hr infusion) or pentobarbital (5mg/kg IV load, 0.5-10mg/kg/hr infusion) to target 24 hours of complete EEG suppression followed by tapering over 12 hours. Medical records and outcomes were reviewed.

Results: Patients' age range was 59-72 years. The initial EKG showed either ventricular fibrillation, PEA arrest or asystole. Time to return of perfusing rhythm ranged from 5-20 minutes. The initial EEG showed rhythmic frequent periodic spikes, and polyspike discharges meeting criteria for non-convulsive status epilepticus. After treatment as above, none of the patients recovered from their status epilepticus and all of them died.

Conclusions: Although the sample size is very small, we have not had significant success in reverting post-anoxic status-epilepticus by aggressive treatment in patients after hypothermia protocol. We are continuing to add more patients.

3.099

TREATMENT OF ELECTRICAL STATUS EPILEPTICUS IN SLOW-WAVE SLEEP WITH HIGH-DOSE ORAL DIAZEPAM

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Rationale: Several small case series have cited high-dose diazepam (DZP) as an effective treatment for electrical status epilepticus in slow-wave sleep (ESES), in the setting of Landau-Kleffner syndrome (LKS) and the syndrome of continuous spike-waves in sleep (CSWS). This

retrospective study was designed to evaluate the short-term efficacy of DZP using a larger cohort, with a standardized protocol for dosage and EEG assessment.

Methods: In a retrospective analysis, 23 subjects were identified with ESES, which was electrographically defined as spike-wave complexes occupying greater than 50% of slow-wave sleep. 12 subjects were male, 11 were female. Mean age was 8 years (range 4-12). Three had LKS whereas 20 had CSWS. All but one had epilepsy, and six carried an autistic spectrum diagnosis. All patients exhibited either language delay or frank language regression prior to diazepam therapy. Patients were admitted for continuous video-EEG monitoring at the Mattel Children's Hospital at UCLA. After overnight baseline EEG assessment, DZP was administered by mouth in a single bedtime dose of 1 mg/kg, and continued for at least three weeks at a dosage of 0.5-1.0 mg/kg/day and subsequently tapered in most cases. Video-EEG was continued for a second night and patients were observed for adverse events. For each patient, ESES was quantified before and after treatment using the spike-wave index (SWI), defined as the proportion of sleep occupied by spike-wave complexes. The change in mean SWI before and after DZP was assessed using a paired t-test.

Results: Mean SWI before DZP was 79.8 (95% CI 75.4-84.3) and mean SWI after DZP was 63.0 (95% CI 55.5-70.6). This represents a statistically significant reduction ($p < 0.001$). Although no standardized neuropsychological assessment was carried out, subjective language performance was uniformly improved among subjects with LKS. However, only modest language improvement was observed among those with CSWS. There were no adverse events that mandated immediate discontinuation of therapy, but several parents reported fatigue and behavioral problems.

Conclusions: Diazepam appears to be a safe and effective means to acutely reduce the severity of ESES, and among patients with LKS, is of at least temporary clinical benefit. Further investigation is necessary to assess the long-term effectiveness of DZP for the treatment of ESES. A blinded and placebo-controlled trial with standardized EEG and clinical outcome measures is necessary to validate these findings.

3.100

SURGICAL PROGNOSTIC FACTOR FOR MRI-NEGATIVE TEMPORAL LOBE EPILEPSY

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Rationale: Magnetic resonance imaging (MRI) cannot always depict the laterality of epileptic hippocampus in patients with temporal lobe epilepsy (TLE). In such cases, epileptic focus is diagnosed based on the extent of interictal epileptic discharges (IED) and the onset of seizure discharges (SD) using intracranial electrodes. Surgical seizure outcome in patients with MRI-negative TLE is poorer than that in patients with hippocampal sclerosis. In the present study, we retrospectively investigated factors affecting surgical prognosis in such MRI-negative TLE.

Methods: We enrolled 15 patients with MRI-negative TLE in this study. Those patients were surgically treated and have been followed up more than one year since surgery. Patients were divided into the following three groups based on the laterality of IED and onset of SD from the video EEG monitoring using intracranial implanted electrodes: 1) IEDs were consistently recorded in unilateral temporal lobe and SDs were emerged from the same side as IEDs (unilateral group, n=6). 2) IEDs were mainly recorded in unilateral temporal lobe, however SDs were emerged from both side of temporal lobe (reverse group, n=3). 3) IEDs were recorded in both side and SDs were also emerged from both side (Bilateral group, n=6). We analyzed the significance of IED and SD for epileptic focus determination from the surgical result of those groups.

Results: We performed the selective amygdalohippocampectomy for the patient whose epileptic focus was located in the non-dominant hemisphere, and the hippocampal transection for the patient with dominant side epileptic focus. In the unilateral group, surgery was carried out the same side of IED and SD, and seizures resolved postoperatively in 5 out of the 6 patients. In the reverse group, surgery was performed on the IED side, but complete resolution of seizures was not observed in any of the 3 patients. In the bilateral group, surgery was performed on the side of habitual seizure onset. Seizure resolution was achieved in 4 out of the 6 patients, moreover seizure frequency decreased in the other 2 patients.

Conclusions: These findings show that seizure outcome is predictably favorable when surgery is performed the side of constant IED and SD. Outcome is also good when surgery was performed on the side of habitual seizure even when IED was recorded bilaterally.

Epileptic focus detection based on origination and spread of habitual seizures is believed to be important for MRI negative TLE patients.

3.101

LONG TERM PROGNOSTIC FACTORS AFTER HEMISPHEROTOMY IN CATASTROPHIC EPILEPSY

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Rationale: This study was designed to evaluate surgical outcomes and prognostic factors that expect more favorable postoperative seizure outcomes after hemispherotomy in catastrophic epilepsy of unilateral hemispheric pathology.

Methods: We performed a retrospective analysis of 26 patients with medically intractable epilepsy undergoing hemipherotomy or functional hemispherotomy at Severance Children's Hospital between 2003 and 2009. Preoperative evaluation included video-EEG monitoring, MRI and FDG-PET. And we also reviewed medical records and postoperative routine EEG findings and confirmative pathologic findings.

Results: Overall mean follow up duration was 2.5 ± 1.9 years and mean duration of epilepsy was 4.6 ± 6.2 years. Mean age of surgery was 5.9 ± 6.3 years and, mean age of seizure onset was 1.4 ± 2.0 years. Sixteen patients (61.5%) showed Engel Class I outcome, 6 patients (23.1%) showed Engel Class II and 4 patients (15.4%) showed Engel Class III outcomes. Preoperative evaluation revealed concordance in 18 patients (69.2%) on MRI and 17 patients (63.0%) on FDG-PET. Malformation of cortical development was the most common etiology (12 patients, 46.2%). Other etiologies included Sturge-Weber syndrome, hemorrhage, infarction, Rasmussen encephalitis, hypoxic ischemic encephalopathy. Overall number of antiepileptic drugs was decreased from 3.38 to 2.15 postoperatively. Among many variables, complete resection was most reliable prognostic factor of favorable seizure outcome ($p=0.0040$) and unilateral abnormality on FDG-PET can be a possible predictor of seizure outcome on univariate analysis($p=0.0135$).

Conclusions: Surgical outcomes of hemispherotomy were favorable. To improve postoperative seizure outcomes, it is most recommended to select optimal candidates of complete lateralized hemispheric pathology through utilization of advanced neurodiagnostic modalities including video EEG monitoring and neuroradiologic studies, especially FDG-PET. With well defined surgery resulted in complete resection, we can achieve more favorable postoperative seizure outcomes in hemispherotomy.

3.102

OBSTRUCTIVE SLEEP APNEA IN AN EPILEPSY POPULATION

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Rationale: Obstructive sleep apnea (OSA) commonly coexists with epilepsy, and treatment of OSA may decrease seizure frequency. It is not clear whether patients with refractory epilepsy have a higher prevalence of OSA. The purpose of this study was to compare the prevalence of OSA in patients with medically refractory vs. well-controlled epilepsy, and to determine whether there are any differences between these two populations concerning age, gender, body mass index (BMI), hypertension, diabetes, and smoking status.

Methods: This is a retrospective chart review study of 286 epilepsy patients, 18-92 years of age, who were seen in consultation at the Comprehensive Epilepsy Center of the Jacobs Neurological Institute, University at Buffalo from 2005 to 2010. All patients had completed the same questionnaire which included Epworth Sleepiness Scale (ESS), seizure frequency (Engel Criteria), smoking status, and other co-morbidities. Patients who had recurrence of any complex partial or generalized seizure in a year despite compliance with seizure medications were classified as medically refractory (Engel seizure frequency of 5 or more). Seizure freedom was defined as lack of recurrence of any complex partial or generalized seizure in the past year. Student t-test was used to compare continuous variables. Chi square test was used for categorical variables to compare OSA, age, gender, BMI, hypertension, diabetes, and smoking status between the two groups. Significance was set at $p < 0.05$.

Results: Out of 286 patients with a diagnosis of epilepsy, 151 (52.8%) were medically refractory by the study criteria, and135 (47.2%) had well-controlled epilepsy. Twenty-two (14.6%) patients with refractory epilepsy and 19 (14.1%) with well-controlled epilepsy had a confirmed OSA diagnosis based on polysomnography data. As previously reported in the literature for general population, we found that in our epilepsy population hypertension, diabetes, BMI > 30 and Age > 50 were significant factors in determining OSA. However, comparing the sub-population of medically refractory and well-controlled epilepsy patients, we did not find any significant difference with regards to the rate of OSA, age, gender, ESS, hypertension, diabetes, or smoking status. The only factor which was significantly different between the two sub-population was higher BMI in medically refractory (mean 28.6) compared to patients with well-controlled epilepsy (mean 26.93, $p = 0.0435$). The use of Continuous Positive Airway Pressure (CPAP) in the medically refractory epilepsy patients with OSA resulted in improved seizure frequency in 5 out of 13 (38%); however, in two of these patients other contributing factors to seizure freedom were identified.

Conclusions: There is a much higher prevalence of OSA in our epilepsy population compared with the general population (14.3% vs. 4.41%). Although we did not find any significant difference of OSA prevalence in our patients with refractory epilepsy and well-controlled epilepsy, treatment of OSA in patients with refractory epilepsy improved their seizure control.

3.103

ALLERGIC RASH WITH GENERIC SUBSTITUTION: WHEN TO LEAVE WELL ENOUGH ALONE

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Rationale: Rationale: The American Academy of Neurology has stated that generic substitution of antiepileptic drugs (AEDS) should not be undertaken without the prescribing physician's approval. The safety concern for this statement has been to prevent breakthrough seizures. The case discussed herein raises an additional concern regarding an adverse effect of generic substitution, which can also be a severe confounder for adequate treatment of an epilepsy patient. This confounder is an allergic reaction to the generic excipient ingredients in a tablet which also contains a potentially allergenic AED.

Methods: Methods: Case presentation-the patient is a 50 year-old Asian woman with a history of localization related epilepsy manifested as complex partial seizures and secondary generalized seizures beginning at age 30 years. Routine EEG showed left temporal spikes and MRI was unrevealing. She was seizure free for seven years taking brand name Lamictal at 500 mg per day. Generic lamotrigine became available during one of her long-term prescription periods and she was changed to generic lamotrigine by the insurance company at the pharmacy and the prescribing physician was not notified. The patient reported that three days after changing to generic lamotrigine at the same daily dose she developed pruritic rash on scalp, neck and torso. The patient was emergently examined by the prescribing physician and found to have confluent red macular rash in the same areas. This was thought to be a drug-related allergic rash, possibly associated with the generic lamotrigine formulation since no other medications had been changed. Due to concern about the risk of seizures, the patient did not want to discontinue lamotrigine. Therefore, she was immediately changed back to the brand name Lamictal (after emergency insurance authorization) and the rash resolved within two days.

Results: Results: The patient had an allergic reaction to the generic formulation of lamotrigine, but no allergy to Lamictal either before or after the allergy to the generic tablet. This isolates an unknown generic excipient as the allergen, rather than lamotrigine.

Conclusions: Conclusion: The forced use of generic formulations by an insurance company could lead to incorrect assumptions about the allergic profile and best treatment approaches for a patient with epilepsy. In this case, the patient was well controlled on brand name Lamictal and was forced by circumstances beyond her control to change to generic lamotrigine. Many treating physicians might not have rechallenged her with the brand name even though she had a long history of seizure freedom due to the concern that she may have developed a lamotrigine allergy. This case demonstrates that it may be in the best interest of the patient to leave well enough alone.

3.104

CHARACTERISTICS OF INTRACTIBILITY IN A COMMUNITY-BASED EPILEPSY SURGERY PROGRAM

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Rationale: Epilepsy surgery is an important clinical option for individuals with medically intractable epilepsy, yet referral for evaluation typically takes 20 years from epilepsy diagnosis. Many barriers to epilepsy surgery have been identified. Aim of this study was to describe the demographics of individuals referred for epilepsy surgery evaluation and treatment in a community-based epilepsy program.

Methods: Among 480 patients referred to the author's epilepsy clinic for intractable epilepsy over two years' time (2008-10), 11 patients, aged 16-73 yrs (mean age 32yrs), were evaluated and treated for epilepsy surgery. 60% of all referrals came from non-neurologists, while all epilepsy surgery candidates came from neurologists. All 11 (2.2%) had medically intractable epilepsy confirmed by video-EEG monitoring. The presurgical evaluation also included clinical evaluation, MRI, ictal and interictal SPECT, Wada testing, neuropsychological evaluation, as well as surgical consultation. The duration of epilepsy was 12 yrs (range 1-30yrs). Four of the patients had presurgical diagnoses of symptomatic epilepsy (2 lesional, 2 mesial temporal lobe sclerosis). All proceeded to focused intracranial monitoring with subdural strips. Localization to the right mesial temporal lobe (3/11) and lesions (2/11) lead to resection. Initial intracranial monitoring lateralized to a frontal seizure focus in over half of the cases (6/11), leading to subdural grid localization and cortical mapping. A single frontal seizure focus was identified in 5/6 patients [2 left, 3 right hemisphere], resulting in combined focal cortical resection and multiple subpial transections. The 6th patient had 2 independent seizure foci in the right mesial temporal and right frontal lobes.

Results: Neuropathology review of all resections identified focal cortical dysplasia (CD) in 5/6 frontal cases [5 Type I & 1 Type IIa CD] (45% all cases). Ectopic neurons were identified in the single case with 2 seizure foci. Hippocampal sclerosis in all 4 mesial temporal lobe resections patients, only 2 of whom had neuroimaging correlate on MRI. The two lesional cases were low grade gliomas.

Clinical follow up of the 11 patients undergoing epilepsy surgery range from 2 yrs to 4 mo (mean 11 mo). Baseline seizure frequency was an average of 4/month (range 2-6). Nine patients (81%) had Engel Class1 outcome, including no auras. The single patient with CD Type IIa had rare sleep-onset seizures, stopped with initiation of a third antiepileptic drug (AED). One of the two patients with low grade glioma had transient break-through seizures after initial early attempt to lower AED dosing. A single significant complication included a subdural hematoma associated with a grid, with no morbidity.

Conclusions: In a small case series, extratemporal/ frontal lobe epilepsy represented a majority of cases referred for clinical evaluation in a community-based program. All surgical cases had abnormal neuropathology findings, with CD representing the common finding. A combination of multiple subpial transections and focal cortical resections was effective in initial follow up.

3.105

EVALUATING THE CONCERNS OF PREGNANT WOMEN WITH EPILEPSY: A FOCUS GROUP APPROACH

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Rationale: Through a multi-year collaboration with the Medical Center's Maternal-Fetal Medicine program, the Comprehensive Epilepsy program works closely with pregnant women with epilepsy. We have observed over the last 7+ years that some women stop or decrease their antiepileptic drug therapy during pregnancy because they fear fetal effects of therapy. This places the woman and her developing fetus at risk for adverse outcome due to increased seizure activity. The rationale of this behavior is not completely understood. The aim of this qualitative project was to determine the concerns of pregnant women with epilepsy via small focus groups where they were interviewed directly.

Methods: Pregnant women with epilepsy were recruited at their routine visits at either the High-Risk Obstetrics Clinic or the Epilepsy Clinic. The 60 to 90 minute sessions were held in collaboration with the Epilepsy Foundation of Central Ohio Social Worker. We conducted 10 separate focus groups over 33 months.

Results: We conducted multiple, asynchronous focus groups with a total of 21 second or third trimester pregnant women. The mean age of the participants was 27.5 (± 5.3) years; with a mean duration of epilepsy of 10+ years. Most women (n=16, 76%) had experienced generalized tonic-clonic seizures. Eleven women (52%) reported seizures within the past 6 months; including 4 women with seizures within the 30 days prior to the focus group. Seventeen women (81%) were prescribed antiepileptic drug monotherapy; with the remaining 4 on polytherapy. Twelve of the 21 pregnancies were unplanned. This was the first pregnancy for seven women. Nine women (43%) reported taking folic acid before they became pregnant. Twelve women reported changes to their antiepileptic drug regimen during pregnancy, six of whom had changes made by their prescriber. Of particular interest, six women (29% of all study participants) self-altered their antiepileptic drug regimen during their pregnancy. All six of the patient-made alterations were either dose-lowering or stopping antiepileptic drug therapy altogether.

Specific concerns that were raised by the participants during the focus groups included: 1) the safety of antiepileptic therapy during pregnancy, 2) potential neonatal complications including inheritance of epilepsy, 3) neonatal management and 4) labor and delivery issues. Additional concerns included the ability to safely operate a motor vehicle and educating their families and children about epilepsy, especially how to respond in the event of a seizure. An unanticipated benefit of these sessions included fostering patient comfort and an opportunity for patient-to-patient teaching and collaboration.

Conclusions: We believe our study adds insight to the concerns of pregnant women with epilepsy. By identifying these concerns, we are able to be more directed in our approach to patient education and ultimately improve outcomes in women with epilepsy.

3.106

RECURRENCE OF SEIZURES IN SREAT AFTER DISCONTINUATION OF IMMUNOMODULATION

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Rationale: Patients with Steroid Responsive Encephalopathy Associated with Thyroiditis (SREAT), also known as Hashimoto's Encephalopathy, may present with seizures. There are no well-established treatment guidelines. Our case series describes patients with this presentation who then develop subclinical seizures. In cases of ongoing encephalopathy it is essential recognize subclinical seizures and to assure they are adequately treated.

Methods: We retrospectively reviewed the clinical presentation, imaging, laboratory analysis and electroencephalography in a series of two patients with SREAT. The setting is the University of Colorado Comprehensive Epilepsy Center, a tertiary referral center in the Rocky Mountain region. Patients were admitted after initial presentation with status epilepticus. We then performed a meta- analysis on all case reports of SREAT published since 1982 to determine presence of seizures and response to treatment.

Results: Including our two patients, there are a total of 34 patients with SREAT in this analysis. Forty-four percent of these presented in status epilepticus. As per definition all responded to high dose steroids. In addition to steroids, 8 others received other immunomodulatory agents including azathioprine (3), cyclosporine (1), methotrexate (2), IVIG (1). 38% regressed with discontinuation of immunomodulation.

Conclusions: The focus of most of these series did not include an analysis of repeat EEG to determine if ongoing encephalopathy or psychosis was the result of increased seizure activity, as was their presenting symptoms. Numerous of these relapsed patients were encephalopathic and in our series both had either definitive seizures and/or hyperirritable cortex on EEG. These results emphasize the need to repeat EEG in cases of relapse of encephalopathy or psychosis and suggest that immunomodulation in combination with antiepileptic drug therapy is needed for good resolution of seizures.

3.107

A PILOT STUDY OF NON-EPILEPTIC SEIZURES (NES): SUPPORT AND EDUCATION AT THE TIME OF DIAGNOSTIC DISCLOSURE

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Rationale: NES are costly to the patient and society because NES are often misdiagnosed, patients are resistant to the diagnosis and they tend to be difficult to treat. This randomized control pilot study evaluated the effect of psycho-educational intervention (PEI) by a psychiatric nurse.

Methods: Nineteen subjects with NES, diagnosed with video-EEG monitoring, were randomly assigned to two groups: specialist PEI (n=9) and treatment as usual (n=10) were compared six to eight weeks after diagnosis on the outcome variable of follow up with a therapist. Additional exploratory outcome measures (QOLIE-31 and Health Care Utilization) were collected.

Results: All nine patients in the PEI group made or kept an appointment, verified by a blinded phone interview 6 to 8 weeks after diagnosis presentation. Only 5 in the treatment as usual group made or kept an appointment ($\div 2 = 6.107$, $p = .033$). At follow up, females in the treatment group have a higher quality of life (63 vs. 37, P=0.015), overall score (29 vs. 21), and social function score (36.4 vs. 22.3) than those of females in the control group. Males decreased in all three scores in the treatment group compared to those in the control group, however the effect is not significant at the 5% level. This difference may be due to confounding factors.

Conclusions: Adequate follow up is a prerequisite to effective treatment and was significantly improved by specialist PEI. The significance of the gender differences is unclear. Two patients in the control group and none in the PEI group expressed disbelief of the diagnosis leading to delay in treatment and possible overusage of medical resources. We conclude that specialist PEI is helpful in the management of patients with PNES.

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3.108

LACOSAMIDE IN PROGRESSIVE MYOCLONIC EPILEPSY TYPE 1: A CASE REPORT; KATHRYN A. POLOVITZ, M.D., MARK SPITZ, M.D

Kathryn A. Polovitz (University of Colorado Neurology, Denver, CO)

Rationale: Background: Progressive Myoclonic Epilepsies represent a group of epilepsies characterized by different seizure types, ataxia, cognitive impairment and myoclonus. These epilepsies are often pharmacologically challenging to treat based on the progressive nature of the disorders.

Methods: Case Report: We present a case of a 42 year-old, right-handed woman who developed epilepsy at approximately age 10. For several years, she was thought to have juvenile myoclonic epilepsy (JME), as her events were described as generalized tonic-clonic seizures, myoclonic jerks with occasional atonic episodes, and absence seizures. However, she continued to have worsening of her events, which is inconsistent with JME, therefore, genetic testing was done. She was found to have progressive myoclonic epilepsy type 1. The severity of her events then worsened to the point of being nearly wheelchair-bound secondary to injuries sustained with her atonic events. She has tried several medications in the past with therapeutic blood levels, including: depakote, topamax, keppra, and lamictal. Also, she had a vagal nerve stimulator placed approximately seven years ago with no drastic change in myoclonic events. In September of 2009, the patient was placed on lacosamide.

Results: Since addition of lacosamide, she and her caregiver have reported a drastic decrease in the myoclonic events, from hourly events before the addition of lacosamide, to approximately three events weekly currently. Also, and we believe most importantly, she has reported a change in her speech with less stuttering and pausing. She reports that "a cloud has been lifted" and she is able to think more clearly.

Conclusions: Lacosamide is a relatively new medication and its efficacy in different kinds of epilepsy is yet to be discovered. We present a case of a patient with progressive myoclonic epilepsy, for whom lacosamide has drastically decreased the number of myoclonic events and has had perceived assistance with cognition.

3.109

THE CURIOUS CASE OF SEIZURE REMISSION IN A PATIENT WITH REFRACTORY BITEMPORAL EPILEPSY: ROLE OF NEUTROPENIA?

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Rationale: Patients with refractory epilepsy typically undergo serial trials of medications in various combinations. In published clinical trials the reported rate of seizure freedom for a three month treatment period upon adding a new drug is only a few percent. Long term remission in highly refractory patients is rarely reported.

Methods: We report a 38 year old caucasian female, followed at UCSD Epilepsy Center from 1994 to present. Her epilepsy began shortly after a coup-contracoup head injury from a horseriding accident at age 20. Post injury head CT showed bilateral temporal contusions; subsequent MRI showed encephalomalacia in the right lateral temporal cortex. Comprehensive workup for epilepy surgery included Video-EEG with scalp and intracranial electrodes, revealing bilateral independent seizure onsets with distinctive features in right and left temporal seizures.

Medication trials included gabapentin, carbamazepine, oxcarbazepine, phenobarbital, vigabatrin (in clinical trial), acetazolamide, zonisamide, valproic acid, primidone, phenytoin, lamotrigine, levetiracetam in various combinations. She had Vagus Nerve Stimulator (VNS) implanted in 2001 with a battery replacement in 2008. Small adjustments in stimulation parameters were made several times per year. Despite up to 4 drugs and VNS, her seizure calendars consistently showed 40 or more simple and complex partial seizures per month, for over a decade. Due to chronic hyponatremia and chronic leukopenia (with adequate neutrophils) her epileptologist tapered her off oxcarbazepine and onto pregabalin in late 2008. By Jan 2009, she took pregabalin 600 mg and remained on levetiracetam 3000 mg, topiramate 200 mg and clonazepam 3 mg daily in 4 divided doses.

Results: Within weeks of the conversion, the patient noted remission of seizures. At her next visit, the CBC revealed stable leukopenia with new neutropenia and absolute neutrophil counts(ANC)of 200-400. She is followed by both a community and university hematologist with a working diagnosis of autoimmune neutropenia. The patient remains healthy despite chronic low ANC. The pregabalin dose has been gradually decreased from 600 mg to 200 mg daily, with continued seizure remission and continued neutropenia. An emergency appendectomy in May 2010 was associated with transient elevation of ANC to >600, which fell quickly postoperatively, but no seizures.

Conclusions: This case provides reassurance that patients with longstanding refractory epilepsy may enter stable remission during continued rotation of drugs in variable combinations, along with VNS. However, we cannot ignore the potential role of neutropenia, which emerged co-incident with remission. While the cause of neutropenia remains under investigation, this observation supports the hypothesis that inflammation may contribute to epileptogenesis (Vezzani et al., 2005, 2008; Choi and Ko, 2008). After 15 years of epilepsy refractory to polypharmacy and VNS, her remission continues at 18 months, and her ANC remains <500. Additional similar cases are sought to further explore this relationship.

3.110

EFFICACY AND SAFETY OF ADJUVANT INTRAVENOUS LACOSAMIDE IN CHILDREN WITH INTRACTABLE EPILEPSY

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Rationale: The aim of the study is to evaluate the safety and efficacy of intravenous Lacosamide in children with intractable epilepsy. The medication offers a novel mechanism of action and new potential for pediatric use. There have been no previously reported case series describing the use of intravenous Lacosamide in the pediatric population.

Methods: After approval from the Institutional Review Board of the University of Chicago, the records of patients with epilepsy treated with Lacosamide from January 2009 to October 2009 were reviewed. Patients less then 16 years old with intractable complex partial epilepsy were included. Age, sex, type of seizures, medication, previous surgery, duration of treatment efficacy and side effects were assessed. No institutional, public, or industry funding was used to develop this study.

Results: 9 patients (5 males and 4 females) met the inclusion criteria for the study. All patients tolerated Lacosamide infusion well. The most common side effect was drowsiness during the initial titration phase. In one patient, serum Valproate levels fluctuated during first 3 days of therapy before stabilizing. Another patient reported exacerbation of insomnia (which had already been a problem prior to Lacosamide therapy). Six patients had reduction in seizure frequency at more than 4 weeks of maintenance therapy. Three patients showed no reduction in seizure frequency; however in one of those we were able to reduce her concomitant Phenytoin dose without any increase in seizure frequency. This patient had a history of requiring high levels of Phenytoin to maintain a mild degree of seizure control. Interestingly, of the three patients who showed no response to Lacosamide, two of them had both complex partial and generalized epilepsy.

Conclusions: To our knowledge this is the first paper in the literature that describes usage of intravenous Lacosamide in children. Our findings suggest Lacosamide may be an effective anticonvulsant medication and highly tolerable even with rapidly escalating doses when given parentally in pediatric patients with refractory epilepsy.

3.111

EFFICACY AND TOLERABILITY OF LACOSAMIDE IN REFRACTORY EPILEPSY

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Rationale: Lacosamide (LCM) is approved as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients aged 16 years and older

Methods: Descriptive observational study. Inclusion criteria: patients aged 16 years and older with refractory epilepsy treated LCM as adjunctive therapy in our Epilepsy Unit from March 2009 to May 2010 with a minimum follow-up the same dose for 3 months.

We analyzed: demographic data , seizure type, epilepsy syndrome, monthly frequency of seizures (two months before and during three months with stable dose), tolerance and concomitant antiepileptic drugs.

Results: 46 patients (17 M, 29 F). Average age: 38 years (22-61). Years of evolution of epilepsy: 23 years (2-50 y). Average frequency of seizures 26 / month (2-120). Mean duration of treatment: 23 weeks (12-60).

Type of crisis: temporal (52%), frontal (30%), occipital (4%), generalized (26%), unclassificable (15%). Epileptic syndrome: MTLE 28% TLE 15%, 30% FLE, OLE 4%, generalized symptomatic epilepsies 10%.

Efficacy: seizure-free 13%, seizure- reduction > 75% 10%, seizure-reduction 50-74% 15%, no changes 26% .

Side effects: 31% (12 patients), but only one discontinuation. 11 patients: related to doses > 800 mg / 24h of CBZ and improved adverse effects with the decreased of this drug. One patient required also LMT decreased.

Conclusions: In our experience, lacosamide is an effective and well tolerated antiepileptic drug on the treatment of patients with refractory epilepsy.

3.112

TOPIRAMATE IS EFFECTIVE FOR STATUS EPILEPTICUS AND SEIZURE CONTROL IN NEURAMINIDASE DEFICIENCY

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Rationale: Sialidosis (OMIM# 256550) is a lysosomal storage disorder caused by a deficiency of the enzyme á-N-acetyl neuraminidase resulting from mutations in the NEU1 gene. Its prevalence is estimated at 0.02-0.05/100,000 live births. We report status epilepticus (S.E.) occurring in a patient with sialidosis type II with good response to topiramate.

Methods: Clinical observations of a patient.

Results: A 16-year-old female patient weighing 30 kg was admitted to our emergency unit due to S.E. She was in optimized treatment with valproic acid 30 mg/kg/day, primidone 10 mg/kg/day, and clobazan 0.20 mg/kg/day. She was still presenting weekly myoclonic seizures when she developed S.E. She was diagnosed with sialidosis type II when she was 7 years old. The patient presented delay in neuropsychological development, short stature, and mild dysostosis multiplex. In the emergency room, we observed the occurrence of seizures about every five to ten minutes. Continuous intravenous midazolam was started and increased to 0.4 mg/kg/hour without any benefit. Extensive evaluation for possible causes of S.E. other than sialidosis was negative. MRI revealed only mild cerebellar and brain atrophy. Seizures, lasting up to 30 seconds, were provoked by tactile stimuli and were characterized by an extensor tonic spasm in the upper and lower extremities followed by tonic arm flexion and facial mimic muscle contraction. These movements were followed by several massive generalized myoclonic jerks. Ictal EEG showed a train of 15 Hz rhythmic spikes, predominantly in frontal regions. This rhythm rapidly evolved to a polyspike-slow wave complex with fast fading away and was then replaced by a generalized depression of background activity. Valproic acid was increased to 75 mg/kg/day without benefit. Next day we introduced topiramate 2.5 mg/kg/day. There was an evident improvement in seizure control and about 8 hours later she was seizure free.

Conclusions: Treatments approved by the United States Food and Drugs Administration (F.D.A.) for the treatment of S.E. are phenytoin, bezodiazepines, barbiturates, and propofol. However, treatment of S.E. in myoclonic progressive epilepsies has not been completely established. Midazolam was not effective in suppressing seizures in the present patient. We could have opted for the use of propofol or barbiturates; however, the patient was already taking barbiturates and had not improved with previous dosage increases. Propofol would be useful during the acute phase but is not an option for long-term seizure control. Phenytoin could aggravate myoclonic seizures, the type of seizure affecting our patient. Newer agents for S.E. treatment might be an interesting option. These drugs are also useful as antiepileptic drugs after S.E. We tried topiramate and it worked. Based on our observations, we suggest that topiramate may be used for the treatment of both S.E. and seizures observed in patients with sialidosis or other forms of progressive myoclonic epilepsies. Further studies are necessary to confirm our clinical observations. This work was supported by CNPq.

3.113

EPILEPSY IN CHILDREN HASHIMOTO ENCEPHALOPATHY

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Rationale: Hashimoto encephalopathy (HE) is a rare cause of epilepsy in children. Patients are usually unresponsive to anticonvulsant therapy. The clinical presentation and natural history of HE in children has been poorly characterized.

Methods: To better characterize the epilepsy in children with HE, a retrospective chart review of all cases of HE seen in children (less than 16 years old) seen during the last five years was performed. Special attention was paid to clinical presentation, EEG, therapy and outcome.

Results: Eight patients (age 1.5 to 15 YO) carried diagnosis of HE: five were female (mean age 10 YO) and three were male (mean age 7.5 YO). Two girls (mean age 9 YO) and one boy (9 YO) had epilepsy. Seizures were preceded by behavior changes in both girls. One girl presented with myxedema before onset of seizure. Behavior changes were a late finding in the boy and alternating hemiplegic migraine occurred after the onset of the first seizure. In the three HE patients with epilepsy, seizures were either generalized tonic clonic or partial complex with status epilepticus, refractory to anticonvulsants, but exquisitely responsive to steroid therapy. EEG shows a focal or generalized encephalopathy. Hypothyroidism required treatment in the 3 HE patients with epilepsy.

Conclusions: Epilepsy can be the first symptom in HE, but behavioral changes frequently precede the onset of symptoms. Status epilepticus with partial or generalized seizures may be the first manifestation.

3.114

NEW ONSET REFRACTORY STATUS EPILEPTICUS

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Rationale: Status epilepticus (SE) is defined as presence of continuous seizure activity for more than 30 minutes or two or more seizures in succession without recovery and return to consciousness in between. Causes of SE include noncompliance or discontinuation of AEDs, trauma to the head, acute structural injury of brain (tumor or metastasis, infection, hemorrhage, cerebral anoxia, etc). This is a case of new onset refractory SE (NORSE), for which no cause was determined despite extensive work-up

Methods: A 23 year old female was admitted to the hospital after she was found unresponsive by a friend. She was unresponsive and febrile on arrival to the ED. While in the ED, she had one episode of generalized tonic clonic seizure. She received dose of lorazepam IV. Preliminary work up in the ED included a CT brain which was normal. A lumbar puncture was performed which showed leukocytosis with neutrophil predominance (WBC 21, with neutrophils 87%). She was admitted to the ICU and treated empirically with acyclovir, vancomycin and cefriaxone. An EEG was performed the next day, which showed diffuse slowing. The next day, she developed frequent complex partial seizures, with head and eye deviation to the left and oral automatisms, which became secondarily generalized. She received valproic acid and levetiracetam IV, in addition to fosphenytoin. She was intubated for airway protection, and started on midazolam drip, and propofol was added in increasing doses, with limited success. Continuous video-EEG monitoring at the bedside revealed frequent seizures arising from the right temporal region initially, and then from either temporal region, with secondary generalization, despite high doses of midazolam, propofol and pentobarb infusions

Results: Cultures for bacteria, virus and fungus were negative in blood and CSF. Tests for cryptococcal antigen, HSV PCR, EBV, West Nile, CMV, toxoplasma, RMSF and HIV were negative. Toxicology profile was negative except for cannabis. NMDA receptor antibody, ACE levels in CSF, ANA, ANCA and anti-HU protein antibodies were negative as well. MRI of the brain was performed twice with and without gadolinium, which did not reveal any abnormalities. Pelvic sonogram did not reveal any ovarian tumors. In addition to continuous infusion of anticonvulsants, she also received a course of IVIG and methylprednisolone, and a dose of pyridoxine. She continued to experience seizure activity despite being on 6 different anti-seizure medications (midazolam, pentobarbital, propofol, phosphenytoin, valproic acid and levetiracetam). Burst suppression was achieved after several days. Each attempt to decrease the dose of any of the medications resulted in recurrence of seizures. The patient died 48 days after admission.

Neuropathology report revealed right hippocampus sclerosis, cerebral edema, transtentorial uncal herniation, pontine hemorrhage and metabolic gliosis

Conclusions: Refractory SE results from excitation of a group of neurons and a failure of centrally mediated mechanisms to suppress the seizure activity. Finding an etiology and understanding the mechanism of NORSE will help to identify new treatment options.

IMAGE: images/906077_A.jpg

Right temporal seizure

IMAGE: images/906077_B.jpg

Management of RSE

3.115

INTRACTABLE EPILEPSY AND SCN1A MUTATIONS: CLINICAL CHARACTERIZATION, TREATMENT OPTIONS AND OUTCOME

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Rationale: SCN1A mutations have emerged as an important cause of epilepsy syndromes. Disturbances of SCN1A gene lead to a disruption in function of the voltage-gated sodium channel alpha subunit type 1, resulting in abnormal sodium currents. (Strafstrom CE, J Child Neurol 2009, 24:S15).The majority of mutations arise de novo and result in a range of phenotypes from generalized epilepsy with febrile seizures (GEFS+) to severe myoclonic epilepsy in infancy (SMEI or Dravet Syndrome). (Fujiwara T, 2006, 70:S223). The relationships of the phenotypes to the various mutations are still being elucidated. (Lossin C, Brain Dev 2009, 31:114) Management of these patients remains challenging, as many patients remain poorly controlled on multiple antiepileptic drugs (AEDs). To our knowledge there is no literature discussing the usefulness of non-medical interventions such as VNS, corpus callosotomy and cortical resection in patients with SCN1A mutations.

Methods: Four children with SCN1A mutations and severe epilepsy were retrospectively reviewed. Type of mutations, age of seizure onset, seizure types, medical and surgical treatments, and outcomes were reviewed.

Results: All patients presented with seizures within the first two years of life. Seizure types include myoclonic, complex partial, generalized tonic-clonic (GTCS), absence, and infantile spasms. All patients are developmentally delayed. Genetic mutations include 1 frame shift, 1 splice site disruption, and two missense mutations. The patient with the frame shift mutation suffers only occasional GTCS and is the highest functioning, and has had a positive response to a sodium channel blocker (oxcarbazepine). Three patients had VNS placement but only one had significant improvement. The other two had subsequent corpus callosotomy (anterior two-thirds in 1 and complete in 1) that resulted in improved seizure control. One of these patients went on to have evaluation with intracranial electrodes and left temporal and orbito-frontal resection, as his seizures became lateralized after callosotomy. Although he has subsequently developed a new seizure focus in the contralateral temporal lobe, his seizure burden remains improved.

Conclusions: Surgical intervention including VNS, corpus callosotomy, and cortical resection in selected patients with SCN1A mutations may be a useful adjunct in amelioration of severe epilepsy. Although a theoretical risk of worsening symptoms has been suggested with AEDs that block sodium channels, they should not be eliminated as treatment options. Further study is needed to better elucidate genotype-phenotype correlations between mutations types and clinical presentations, and to determine ideal candidates for surgical

interventions. Long-term follow-up is also necessary to document extended benefit.

3.116

IMPROVING THE PATIENT EXPERIENCE FOR FAMILIES WITH CHILDREN UNDERGOING VAGUS NERVE STIMULATION THERAPY: A QUALITATIVE STUDY

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Rationale: To examine the experience of parents with children undergoing Vagus Nerve Stimulation (VNS) therapy following changes made to service delivery as a result of informal feedback from parents dissatisfied with aspects of clinical coordination/continuity of care.

Methods: To improve the patient experience changes were introduced, namely: a patient pathway algorithm; patient information leaflet; teaching package for clinical staff and extending the role of the specialist nurse to include responsibility for managing admission, discharge and follow up outpatient care. Parents of twenty six children (12 female), age range 5-17 years (mean age 12.8 years), with drug resistant epilepsy who underwent VNS therapy at Great Ormond Street Hospital during 2008-09 were asked to fill in a questionnaire about their experience of the service. The questionnaire asked about child and family preparation; hospital stay and follow up outpatient care.

Results: All parents reported satisfaction with written and verbal information received and with their child's hospital admission, stay and discharge. Twenty two out of 26 parents reported satisfaction with the organisation of outpatient appointments. Four parents reported receiving more than one outpatient appointment letter causing confusion. There was a high degree of satisfaction with quality and continuity of outpatient clinical care with no perceived difference in care when seen by either the consultant paediatric neurologist or the specialist nurse. Written comments from parents highlighted the value parents placed on the role of the specialist nurse in providing clinical continuity through the patient pathway from hospital admission, discharge and follow up outpatient care.

Conclusions: Our findings suggest that developing an algorithm, improving written patient information, developing a staff teaching package and extending the role of the specialist nurse in managing the patient pathway can improve parental satisfaction with VNS care.

3.117

ELECTRICAL STATUS EPILEPTICUS DURING SLOW SLEEP: A REVIEW OF 7 PEDIATRIC CASES

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Rationale: Electrical status epilepticus during slow sleep (ESES) is a rare epileptic syndrome with a characteristic continuous spike-waves electroencephalographic pattern during slow sleep (CSWS). These patients can present with either obvious clinical seizures, or a developmental regression. Here we report seven cases of ESES diagnosed during the year 2009 as well as the response to different treatment strategies.

Methods: During the year 2009 seven patients with previously controlled epilepsy (2-3 anti epileptic drugs), presented for recurrence of seizures (day and night in 5 patients) and for learning regression (in 2 patients). A 24 hour video EEG monitoring was performed in all these patients

Results: All these patients showed an EEG pattern with CSWS and met the clinical criteria of ESES. The age ranged between 2 and 9 years. The patients presented either generalized or partial epilepsy. Three of these patients had symptomatic epilepsy (hypoxic ischemic encephalopathy, head trauma, dural sinus thrombosis with intraventricular hemorrhage), one with cryptogenic epilepsy, and three with idiopathic epilepsy. The first seizures were noted as early as 10 days of age in one patient, and as late as 9 years of age in the oldest patient.

Two patients were treated with Hydrocortisone (5mg/kg/day) for 3 months, one patient was given intra venous Methylprednisolone (three courses of 30 mg/kg/day for 3/7 consecutive days) followed by a course of prednisone 2 mg/kg/day for one month. Three patients were given oral Prednisone (2mg/kg/day) for 3 months. Clinical improvement was noted in 4 patients, no clinical seizures were noted in the following three months, and three patients showed 50-80 % improvement of the EEG electrical activity.

Conclusions: Electrical status epilepticus during slow sleep is one of the epilepsy syndromes, even though rare; yet, easy to diagnose, and should not be missed in front of a decompensation epilepsy, or an acute learning regression. The traditional anti epileptic drugs tend to fail, but these patients present a good response to corticoid therapy in most of the cases.

3.118

LAMOTRIGINE IS FAVORABLE FOR STARTLE-INDUCED SEIZURES

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Rationale: Falling due to startle-induced seizures (SISs) often leads patients to injury. The triggers of SIS are unexpected visual, somatosensory, or auditory stimuli, which are too common to avoid in daily life. As SISs are often refractory to medication, effective therapeutic option is desired.

Methods: We report three patients whose SISs were significantly improved by lamotrigine (LTG), liberating patients from restricted daily life. Follow-up periods ranged from three months to one year.

Results: (Patient 1) A 19 year-old male with mild mental retardation. The onset of epilepsy was at seven months. His seizure was sudden tonic extension of the arms and legs induced by unexpected sound, visual or touch stimulus. He fell down due to SIS from five to ten times per day with frequent injury. Interictal EEG showed spikes predominant on left frontal region. Ictal EEG showed bilateral diffuse attenuation. MRI showed mild diffuse cerebral atrophy. SISs decreased to once a month after adding LTG 200mg to VPA and CLB. Seizure reduction made him free from crawling all day. (Patient 2) A 51 year-old female. The onset of epilepsy was at 8 years. Sudden tonic extension of all limbs induced by unexpected sounds frequently struck her down to the floor. Ictal EEG showed bilateral polyspikes over F-C-P area followed by diffuse attenuation. MRI demonstrated mild diffuse cerebral atrophy. Addition of LTG 150mg to CLB, ZNS and PHT

reduced her several daily SISs to less than once a day and dramatically improved her life. (Patient 3) A 7 year-old female with post-encephalitic epilepsy. Ictal EEG showed bilateral diffuse polyspikes followed by attenuation. MRI revealed diffuse cerebral atrophy predominantly on bilateral frontal lobes. Her seizures occurred around one hundred times a day. After adjunctive LTG 20mg to VPA, the severity of SISs became milder enough for her to escape injury, although seizure frequency did not decrease.

Conclusions: LTG is potentially effective for the treatment of SISs and may prevent falling. LTG should be considered to be an option for SISs.

3.119

ADD-ON LACOSAMIDE IN REFRACTORY FOCAL EPILEPSY. WHICH OTHER AED?

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Rationale: The mechanism of action of lacosamide (LCM) is related to slow inactivation of sodium channels. It is not known at this stage whether its efficacy is mostly associated with antiepileptic drugs (AED) with a particular mechanism of action.

We try to determine if LCM is more effective when associated with AED blocking sodium channels or other AED.

Methods: Descriptive, observational study. Inclusion criteria: patients older than 16 years, refractory focal epilepsy treated with LCM as add-on therapy, stable doses for at least three months and a reduction in seizure frequency of at least 75%

We analyzed: demographic data, seizure type, epileptic syndrome, monthly frequency of seizures (two months before and during 3 months with stable doses), tolerance and mechanism of action of AED

Results: We studied 16 patients (5M, 11W) with reduction of seizures greater than 75%: mean age 33 years, average time of evolution: 21 years, mean seizures: 27 per month, average duration of therapy: 23 weeks.

Epileptic syndrome: MTLE 31%, 43% TLE, FLE 6.5%, OLE 6.5%, 6.25%

In 62.5% of patients LCM was associated with a sodium channel blocker AED (CBZ 80%, LMT 20%); the remaining 37.5% of patients associated LEV.

Conclusions: In our study, lacosamide appears to act more effectively associated with sodium channel blockers AED in refractory focal epilepsy

3.120

LONG-TERM OUTCOME OF ETHOSUXIMIDE, VALPROIC ACID, AND LAMOTRIGINE, IN CHILDHOOD ABSENCE EPILEPSY : A SINGLE CENTER OBSERVATIONAL OUTCOME STUDY

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Rationale: To evaluate the long-term efficacy and tolerability of ethosuximide (ESX), valproic acid (VPA), and lamotrigine (LTG), as an initial monotherapy in childhood absence epilepsy.

Methods: The medical record of 84 patients (30 boys, 54 girls) diagnosed as childhood absence epilepsy at Seoul National University Hospital were reviewed retrospectively. Patients with typical absence seizure, characteristic EEG finding (2.5~4Hz spike and wave complex), seizure onset between 4 and 10 years of age, and patients with minimum follow up duration after the treatment more than 1 year were included. Treatment outcome was defined as freedom from treatment failure including freedom from failure due to adverse events.

Results: ESX, VPA, and LTG were administered to 35, 35, and 14 patients, respectively. After 3 months of treatment, the freedom from failure rates were 83% (29/35) in ESX group, 77% (27/35) in VPA group, and 50% (7/14) in LTG group. After 12 months, the freedom from failure rates were 80% (28/35) in ESX group, 69% (24/35) in VPA, 43% (6/14) in LTG group. The failure from adverse events was most frequently observed in VPA group (20%, 7/35) compared with ESX (14%, 5/35) and LTG (7%, 1/14) after 12 months. However, statistical analysis could not demonstrate these tendencies except the better treatment outcome in ESX group than LTG group.

Conclusions: ESX seems to be more efficacious and tolerable than VPA and LTG in childhood absence epilepsy for long-term treatment. Relatively low efficacy of LTG and high adverse event rate of VPA should be considered when selecting antiepileptic drugs other than ESX.

3.121

ELECTRORETINOGRAM CHANGES IN A PAEDIATRIC POPULATION WITH EPILEPSY - IS VIGABATRIN ACTING ALONE?

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Rationale: Background: Vigabatrin, a structural analogue of the inhibitory neurotransmitter GABA, is widely used as initial monotherapy in patients with infantile spasms and as add on therapy in patients with partial onset seizures. Vigabatrin is associated with retinal toxicity causing constriction of the visual field.

Objective: To assess what effect add-on AED therapy has on the incidence of retinal toxicity in patients being treated with vigabatrin.

Methods: Single centre retrospective study of patients treated with vigabatrin at our centre from Jan 1999 until Dec 2009. Medications received, the dosages and duration of treatment were examined and correlated with ERG results.

Results: ERG results were recorded for 247 patients included in the Ophthalmology database during this 10 year period. Adequate data to allow for definition of toxicity was obtained for 160 patients. Toxicity was detected in 18 of these 160 patients (11.25%). 14 (77%) were in the group treated with additional AEDs, the other 4 received VGB as monotherapy

Conclusions: The prevalence of toxicity detected by ERG was 11.25% among 160 patients assessed adequately. We detected a significantly higher percentage of toxicity in the group of patients treated with VGB and additional AEDs (p=0.018). Our numbers were not sufficient to detect which AED or combination of AEDs which might be associated with higher risk.

3.122

EFFICACY AND TOLERABILITY OF VIMPAT IN PATIENTS WITH INTRACTABLE EPILEPSY

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Rationale: Epilepsy is a seizure disorder that affects approximately 1.2 million Americans. Of these, 70% have partial onset seizures. 30% of these individuals remain medically intractable. For these patients who have failed multiple classes of antiepileptic drugs (AEDs) and/or surgical procedures, newly FDA-approved drugs are of particular interest. Vimpat, a 2nd generation antiepileptic drug with two novel mechanisms of action, was approved in 2008 in United States as adjunctive therapy in the treatment of partial onset seizures. We hypothesize that per oral Vimpat will be efficacious and safe for use in the reduction of number of seizures in patients with intractable epilepsy.

Methods: A retrospective chart review was conducted on all patients with intractable epilepsy who received Vimpat at Scott & White Neurology Clinic/ Texas A & M Health Science Center, Temple, TX between October 2008 and June 2010. Effectiveness was evaluated by comparing seizure frequency of patients with intractable partial epilepsy on their prior AEDs to the seizure frequency after adding Vimpat to their treatment regime. The study patients were followed for a period of 3-12 months following the addition of Vimpat. Subject data were acquired from electronic medical records. Approval for this retrospective analysis of patient records was given by the hospital's Institutional Review Board.

Results: We retrospectively analyzed 10 patients who received Vimpat for intractable epilepsy. The study population consisted of 10 patients (mean age: 44 years, range: 16 - 75 years). All patients had partial epilepsy. Subjects were initially treated with 50 mg/kg p.o. b.i.d. of Vimpat . If Vimpat was tolerated and the patient's seizures were not well controlled , the dosage was increased to 100 mg p.o. b.i.d The study patients have failed an average of 4.1 antiepileptic drugs (range 1-8). (20%) became seizure free following initiation of Vimpat . The 8 patients who were not seizure free on Vimpat showed an average decrease of 64% in number of seizures per month. The monthly seizure frequency was reduced in all patients by at least 50% (range 50-100%). No immediate or long term side effects were reported. Duration of follow up was 3 - 12 months.

Conclusions: Our data analysis suggest that Vimpat may be safe, efficacious, and well tolerated in reducing the frequency of seizures in intractable epilepsy patients who have failed multiple anticonvulsants.

3.123

NEURODEVELOPMENTAL OUTCOME IN CHILDREN EXPOSED TO ANTIEPILEPTIC DRUGS IN UTERO

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Rationale: To assess age appropriate development (social, fine motor, language, and gross motor) in children exposed to antiepileptic drugs (AEDs) in utero.

Methods: We conducted a chart review and identified 31 patients who were treated with antiepileptic medications at our institution during their pregnancy. Children of 22 of these patients fit our selection criteria which included the age range from 4 months to 6 years, and exposure to AEDs for the entire duration of pregnancy. We administered a questionnaire via the phone to assess the children's developmental progress based on Denver Development Scale at the current age. Potential confounding factors were accounted for.

Results: Of the children evaluated for development, 4 of them were exposed to Valproic Acid, 1 to Valproic Acid and Gabapentin, 5 to Lamotrigine, 4 to Carbamazepine, 1 to Oxcarbazepine, 5 to Levetiracetam, 2 to Levetiracetam and Zonisamide, 1 to Levetiracetam and Carbamazepine and 1 to Levetiracetam and Topiramate. All the pregnancies were uncomplicated. There was no toxin or alcohol exposure across the sample size. Based on the Denver Development Screening Test, only 4 children were found to have delays (1 kid was exposed to Valproic Acid and Gabapentin, 2 exposed to Valproic Acid, and 1 exposed to Levetiracetam). One child exposed to Valproic Acid and Gabapentin had mild delays noted in the personal-social skills and language skills at the age of 5 years and 9 months placing him/her at 5 year mark. This child's mother has mild mental retardation and bipolar disorder. The second child found to have delays was also exposed to Valproic acid, and at 4 years and 9 months of age was found to have significant delays in personal-social skills. The child was also diagnosed with autism at 2 years of age. His/her parents have college degree. The third child exposed to Valproic acid, had mild speech delays at age of 4 years placing him/her at 3 year mark. His/ her parents have high school level of education. The mothers of these 3 kids had no seizures during pregnancy. The child exposed to Levetiracetam had mild speech delays at age of 5 years placing him at 4 year mark. The mother of this child had frequent non-convulsive seizure-like events deemed to be non-epileptic in nature based on video EEG monitoring. His/ her parents have college degree. All 4 kids with delays were not exposed to any medications in-utero other than AEDs.

Conclusions: It is challenging to treat pregnant women with epilepsy because there is not enough data as to the effects of individual AEDs on children born to those mothers. Recent studies have shown Valproic Acid exposure to carry the risk of developmental delay and cognitive impairment. Our retrospective analysis shows similar results. Our results need to be interpreted with caution considering the small sample size. Future prospective studies with larger sample sizes for individual drugs are needed to reach statistical significance about the effects of individual AEDs on neurodevelopment outcome.

3.124

ADULTS WITH EPILEPSY IN TERTIARY CARE: RISK FACTORS, SEIZURE TRIGGERS AND PSYCHIATRIC COMORBIDITY

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Rationale: Systematic analyses of patients with epilepsy referred to tertiary care are infrequent. We explored clinical features, epilepsy risk factors, seizure triggers and psychiatric comorbidity, in a large self contained newly referred population.

Methods: The University of Calgary Division of Neurology is the main tertiary referral centre for adults with epilepsy, serving 1.3 million people. We prospectively captured data on all consecutive 1st encounters in our outpatient epilepsy program, using a validated data capture and verification system, excluding patients with single seizures and children. We analyzed demographics, causes of epilepsy, syndrome and seizure type, seizure triggers, and psychiatric comorbidity and its treatment.

Results: In 687 consecutive patients (52% women), mean age and duration of epilepsy was 40 and 12 years, respectively, 23% had an abnormal neurological exam, 83% were on AEDs, and 21% were seizure free in the last year. The majority of patients had focal epilepsy (64%), while 23% had idiopathic generalized epilepsy and 10% had non-epilepsy diagnoses (syncope, psychogenic, others). Primary or secondary generalized tonic clonic (GTC) seizures occurred in 67%. Focal seizures occurred in 55%. The probability of having at least monthly seizures was 70% for simple partial, 54% for complex partial, 56% for GTC and 60% for absences. The probability of having daily seizures was highest for absence (31%), tonic (47%), atonic (40%), myoclonic (39%) and psychogenic (36%) seizures. The most common risk factors for epilepsy were head injury (40%) and family history of seizures (30%), followed by developmental disorders (13%), perinatal factors (7%), stroke (6%), and brain tumor (6%). The most commonly described seizure triggers were stress (82%) and sleep deprivation (70%), followed by non-adherence to AEDs (18%), alcohol (17%) and menses (17%). Psychiatric comorbidity was present at the time of the 1st visit in 28%, and in the past in 23%. The three most common self-reported past psychiatric comorbidities were depression (16%), alcohol/drug dependence (7%), and anxiety disorder (4%). The two most common comorbidities at the time of the 1st visit were depression (14%) and anxiety (7%). Treatment for psychiatric comorbidity was received only by 65% of patients with past comorbidities and by 55% of those with current comorbidities. 7% of patients reported a learning disorder and 30% reported other significant medical conditions.

Conclusions: This consecutive sample provides a good approximation to a population based cohort receiving care at a tertiary care epilepsy program. The general clinical features are similar to other reported series, but GTCs were more frequent. Head injuries and family history were the most important risk factors in this adult population. Factors requiring further exploration include psychiatric comorbidity which was frequent and often untreated, stress as a common and treatable seizure trigger and the lack of AED therapy in 20% of patients.

3.125

ABLATIVE TEMPORAL LOBE EPILEPSY SURGERY SHOULD BE CONSIDERED IN PATIENTS WITH A PRE-EXISTING LIVER TRANSPLANTATION

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Rationale: An estimated 100,000 patients are eligible for epilepsy surgery in the United States. In controlled trials, ablative surgery has been shown to be superior to medical therapy. In ideal patients seizure free outcome can be as high as 80% to 90%. However, despite these numbers there is question of whether epilepsy surgery should be performed in people with significant, chronic, medical conditions such as liver transplantation. There were more than 6,300 liver transplants performed in 2008. Five year survival following liver transplantation is 72%.

Methods: We present three people who first underwent liver transplantation and years later had a temporal lobectomy.

Results: Patient #1 had neonatal hepatitis at age 6 weeks, which led to a liver transplantation at age 4. She was treated with OKT3 which resulted in status epilepticus. She developed mild developmental delay and obsessive compulsive disorder and seizures. Prior to surgery she had complex partial seizures every two weeks. At age 25, she had a right temporal lobectomy. On pathology she had mesial temporal sclerosis. After discharge she became seizure free for two years. Patient #2 began having rare complex partial seizures at the age of 7. In adulthood they gradually accelerated and usually secondarily generalized. She would have 5 - 8 seizures a month. An MRI at age 40 showed a left temporal lobe lesion. She had a lesionectomy and a ganglioglioma was found. Her seizure frequency did not change after this procedure. She developed autoimmune hepatitis at age 50 which led to a liver transplantation. At age 57, she had further resection with a left anterior temporal lobectomy. This resulted in an improvement with her experiencing only nocturnal generalized seizures, 1 per month. Medication adjustments were done with her anti-convulsants and prednisone and she has been seizure free for 6 months. Patient #3 began having rare complex partial seizures at age 10. At age 47 he had liver transplantation for hepatitis B. In the 15 years of follow-up he had no recurrence of hepatitis or significant liver rejection. His epilepsy became pharmacologically intractable, experiencing 1 seizure per week. He underwent a right temporal lobectomy at age 55. Hippocampal sclerosis was found on pathology. In the 6 years following his ablative brain surgery he has had multiple simple partial seizures but only a single complex partial seizure.

Conclusions: In patients without significant pre-existing medical conditions the literature strongly supports ablative epilepsy surgery in appropriate candidates. Since liver transplantation is not a rare procedure, we expect that there will be patients with pre-existing liver transplantation who may also be excellent candidates for an epilepsy surgery evaluation. Liver transplantation has good long term survival and should not necessarily be a contraindication. We have successfully performed ablative surgery in three patients with prior liver transplantation. We have allowed these patients to take advantage of two surgical procedures which independently have an excellent success rate.

3.126

PHARMACOTHERAPY OF NON-IDIOPATHIC PARTIAL EPILEPSIES BASED ON PRECISE SEIZURE SYMPTOMS: A PROSPECTIVE STUDY

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Rationale: Treatment of non-idiopathic partial epilepsies (NIPE) is traditionally based on the seizure (Sz) type of simple partial, complex partial and secondarily generalized seizures, however, this often fails to obtain good Sz control, particularly in chronic epilepsy. We have reported that the effective AEDs differ among precise seizure

symptoms (PSSs) in NIPE by retrospective study of 209 cases of NIPE including 200 cases of chronic epilepsy, that were treated for one year or longer (28th IEC, Budapest, 2009). They consisted of 170 cases of frontal lobe epilepsy (FLE), 28 cases of temporal lobe epilepsy (TLE), and 11 cases of parietal or occipital lobe epilepsy (PLE/OLE). 127 cases had one PSS, 70 cases had two PSSs and 12 cases had three PSSs. AEDs with excellent responder rate (RR>75%: E-RR), good RR (RR=50-74%: G-RR) and poor RR (RR<25%: P-RR) were analyzed in AEDs administered to > 10 cases for each PSS. AEDs with E-RR, G-RR and P-RR for tonic Sz (total 405 trials) were ZNS/potassium bromide (KBr), PB/PHT/CLZ, and CBZ/VPA, respectively. AEDs with these were: for secondarily generalized tonic-clonic Sz (122 trials), ZNS/CZP, PB/PHT/CBZ, none; for clonic Sz (56 trials), CBZ, none, none; for hypermotor Sz (93 trials), PHT, CBZ, ZNS/VPA; for atonic or negative myoclonic seizure (103 trials), ZNS/PB, none, CBZ/CLB/CZP/VPA; altered consciousness or motion arrest (82 trials), CLB/CBZ, CZP, VPA; others including sensory or non-tonic versive seizures (39 trials), none, CBZ, none. To confirm these results, prospective study was conducted.

Methods: Another 83 cases with chronic NIPE, consisted of 70 cases of FLE, 5 cases of TLE and 8 cases of PLE/OLE, were prospectively treated for six months or longer with AEDs with E-RR and G-RR for each PSSs obtained from the retrospective study.

Results: The 50% or greater Sz reduction was obtained in tonic Sz in 38/40 trials with ZNS, 13/13 with KBr, 19/26 with PB, 7/15 with PHT and 4/4 with CLZ. This reduction was obtained in secondarily generalized tonic-clonic Sz in 6/8 with ZNS, 0/1 with CZP, 7/8 with PB and 3/9 with CBZ; in clonic Sz, 10/11 with CBZ; in hypermotor Sz, in no trial with PHT and 0/1 with CBZ; in atonic or negative myoclonic seizure, in 12/12 with ZNS, 1/2 with PB; in Sz showing altered consciousness or motion arrest, in 6/13 with CBZ, 6/10 with CLB and 1/4 with CZP; in sensory Sz or others, in 2/4 with CBZ.

Conclusions: Although more cases are needed to make results firmly, particularly for hypermotor Sz, Sz of altered consciousness or motion arrest, and sensory Sz or others, the present prospective study essentially confirmed the results of the previous retrospective study that the effective AEDs for NIPE were different among PSSs and which AEDs were effective for each PSS. These findings may improve pharmacotherapy of NIPE.

3.127

TOPIRAMATE IN REFRACTORY STATUS EPILEPTICUS: EXPERIENCE FROM A TERTIARY CARE CENTER

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Rationale: Topiramate (TPM) is not widely recognized as an efficacious drug in refractory status epilepticus (RSE). Our experience with use of TPM as an adjunctive antiepileptic drug (AED) in RSE has been positive. We sought to define characteristics and outcome data of our RSE patient population treated with TPM over the past seven years.

Methods: Retrospective analysis of patients identified as having RSE between 2003 and 2009 was performed via chart review. After exclusions (use of TPM at the onset of RSE, any AEDs other than continuous IV anesthetics or benzodiazepines used after TPM initiated, incomplete patient data), 23 patients were identified as having been treated with TPM for RSE. Data collected on each patient included age, gender, history of prior seizure disorder, acute medical management, number of days spent in RSE before and after administration of TPM, and final disposition of the patient. Descriptive data were summarized and analyzed using SPSS for patient characteristics and outcome variables.

Results: Of the 23 patients in RSE, 9 (39.1%) were male, and 10 (43.5%) had a history of seizures. Roughly one half (52%) had non-structural etiologies vs. 30.4% with structural etiologies; 17.4% were idiopathic. Median time spent in RSE was seven days and 14/23 (60.8%) were in RSE 48 hours or less prior to use of TPM. All had failed a typical initial treatment regimen including a combination of benzodiazepines, propofol, and either phenytoin or loading doses of their home AEDs.

In 11 (47.8%) patients, cessation of RSE occurred within three days of initiating TPM. In 20/23 (87%) patients, cessation of RSE was documented within one week. A majority (17/23 or 73.9%) received TPM dosing of 100 mg every four or six hours; four of these patients were given an initial single loading dose prior to the scheduled dosing.

Disposition to home was documented in 4/23 (17.4%) patients, to in-patient rehabilitation in 2/23 (8.7%), and to either skilled nursing or long-term acute care facilities in 12/23 (52.2%). Five patients (21.7%) died in our group: in four patients, care was withdrawn because of prolonged medical complications; one patient had respiratory arrest following extubation. Termination of RSE was documented in these five patients prior to their death.

Conclusions: To our knowledge, this is the largest reported group of patients who were successfully treated with TPM for RSE. Previous reports have established mortality rates as high as 26% in SE (DeLorenzo, 1996) and >30% in RSE (Towne et al., 2003). Mortality in our group treated with TPM was 21.7%. Of the five patients who expired in our study, the immediate cause of death was not RSE; each of these patients had documented cessation of their seizures prior to death. Few data are available regarding medications that may be efficacious in RSE; our study suggests that TPM has potential efficacy in this patient group, possibly due to its multiple mechanisms of action.

3.128

ANALYSIS OF PROGNOSTIC FACTORS OF VAGUS NERVE STIMULATION FOR REFRACTORY EPILEPSY-REVIEW OF 40 CASES

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Rationale: Study of prognosis factors of vagus nerve stimulation (VNS) treatment for refractory epilepsy.

Methods: Retrospective analysis of VNS treatment of refractory epilepsy patients in our center from June 2004 to June 2010 with seizure frequency, attack duration, follow-up period, drug treatment and condition, seizures type and the stimulate current parameters of final follow-up.

Results: Efficiency of 64.3%, 68.9% of children reduce the number of epileptic seizures by 50%, adults 52.3%. 18 cases followed up for more than two years, 6 cases (33.3%) seizures reduced by more than 50%. Overall implant age and age at onset of the effects are statistically significant. The main side effects are hoarseness and cough.

Conclusions: Adults, pediatric patients may be more effective and better; other factors, the impact of the latter is still not entirely clear.

3.129

THE HISTORY OF THE FDA 80-125 RULE FOR BIOEQUIVALENCE OF GENERIC DRUGS INCLUDING AEDS

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Rationale: During the past two decades concerns have been raised about the safety and efficacy of generic AEDs. The +/- 20% range allowed for generic approval is often cited as being too broad. The decision process of how this range was selected may inform future study of generic AED bioequivalence.

Methods: Extensive review of the literature and FDA documents obtained through a Freedom of Information Act request.

Results: Confidence intervals (CIs) were first proposed for bioequivalence testing in 1972. In the early 1970's the basic bioavailability assumption was enunciated: bioequivalent products must have similar rates and extent of availability of active ingredient in the blood. The pharmacokinetic measures were identified as the concentration maximum (Cmax) to assess rate and area under the curve (AUC) to assess availability.

Hypothesis testing was deemed to be inadequate because two equivalent products could be statistically different when only a few percent separated the pharmacokinetic measures if a large enough sample size was used.

During the 1970's-80's numerous authors proposed that bioequivalence would be established if the 90% CIs of the ratios of the means of the Cmax and AUCs of the generic and reference (usually brand) product were within a specified range. The example ranges provided were typically 15% or 20%. No randomized clinical trials were performed to determine the validity of any range. Many of the authors cautioned that the appropriate range may differ for different drugs and that the selected range should be based on individual drug clinical factors.

In the late 1970's, the +/- 20% range was proposed by the FDA. At the time a different method, the 75/75 rule, was used to determine bioequivalence. In 1986 the FDA held a 'Bioequivalence Hearing.' The hearing's conclusion was:

"…differences of less than 20% in AUC and Cmax between products in normal subjects are unlikely to be clinically significant in patients. Clinical studies of effectiveness have difficulty detecting differences in dose of even 50-100%. Few drugs are given on a mg per kg basis to account for weight differences and few drugs have their dosage adjusted in actual clinical practice for factors that may affect blood level concentrations in individuals. Thus, the variability inherent in medical practice and biological variation may cause plasma levels to vary in individuals by much more than 20%."

"Because experts conclude that differences of less than 20% in mean AUC between brand name and generics are rarely unacceptable, FDA has established procedures to assure with high probability that the true mean AUC between brand and generic products do not differ by more than 20%."

Subsequently, the FDA adopted the +/- 20% range, modified to be that the log-transformed 90% CI of the generic product needed to be within 80-125% of the reference product in an average bioequivalence study.

Conclusions: The selection of 80-125% for the allowable range of the 90% CI required to be met by generic drugs, including AEDs, was based on expert opinion and has never been studied in a randomized clinical trial.

3.130

BASAL GANGLIA INJURY DUE TO PRIOR TEMPORAL LOBE SURGERY: VARIABLE EXPRESSION OF MOVEMENT DISORDER AFTER SUBSEQUENT EPILEPSY SURGERY IN CHILDREN

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Rationale: Basal ganglia (BG) injury is a rare but well-recognized complication of temporal lobectomy. In the setting of temporal lobe (TL) tumors, the risk of this complication is increased due to distortion of normal anatomy and vasculature near the temporal stem. However, little is known about the long-term sequelae after such injury, the effects of epilepsy, or the results of subsequent epilepsy surgery on movement disorder (MD). We describe two children with medically intractable epilepsy (MIE) due to temporal lobe tumors, who presented with BG strokes after partial tumor resection. Both patients experienced significantly different MD outcomes before and after subsequent TLE surgery.

Methods: A retrospective review of patients with TL tumors and MIE, who had been referred to the Comprehensive Pediatric Epilepsy Center at Beth Israel Medical Center in New York, was performed. Two patients were identified who had suffered basal ganglia strokes as a complication of prior temporal lobe tumor surgery at other institutions. Pre and post-operative evaluations included VEEG, MRI, PET scans, fMRI, and follow-up with MD specialists.

Results: A 19 yo M (Pt 1) and a 5 yo F (Pt 2) were included in this study. Duration of epilepsy was 14 years in Pt 1 and 4 years in Pt 2. Pt 1 had undergone prior TL tumor surgery at age 10 followed by epilepsy surgery at age 12, which was complicated by traumatic BG injury; at presentation to our institution, he suffered from disabling complex partial seizures (CPS) of 14 years duration, and severe dystonia of the LUE refractory to botulinum toxin. Pt 2 had undergone left temporal tumor resection at age 1, complicated by BG infarction; she presented to our institution with a right hemiparesis and medically intractable simple and CPS involving the RUE (50/day). Both children had a decline in school performance and deterioration in cognitive and language measures on neuropsychological testing. Under our care, Pt 1 underwent staged epilepsy surgery including right anterior temporal lobectomy (ATL) and amygdalohippocampectomy (AH), and has been seizure free (Engel IA) at 5 years F/U. After epilepsy surgery, dystonia has decreased dramatically, with only residual stiffness of the left hand. Pt 2 underwent staged epilepsy surgery at our institution, with a left ATL, AH, and frontal disconnection. She is seizure free (Engel IA) at 1 year F/U, but in contrast to Pt 1, a MD characterized by choreoathetosis of the RUE manifested after epilepsy surgery. Both patients have had significant improvement in language and cognitive measures.

Conclusions: The relationship between MD and epilepsy is poorly understood. Our two patients with MIE and benign temporal tumors experienced significantly different MD histories after BG stroke and subsequent epilepsy surgery. Distortion of mesial temporal structures by tumor, age at the time of injury, degree of BG damage, and extent of subsequent epilepsy surgery are postulated to play a role in the variable expression of MD in this setting.

3.131

SEIZURE CONTROL IS ONE OF MANY FACTORS DETERMINING THE QUALITY OF LIFE IN EPILEPSY PATIENTS

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Rationale: Despite evidence that quality of life in epilepsy patients is multifactorial, many healthcare providers continue to view effective seizure control as the single main determinant of successful treatment. In this study, we aim to: 1- characterize the quality of life in a cohort of outpatients with epilepsy, and 2- evaluate the factors influencing it.

Methods: Since November 2008, the Cleveland Clinic Epilepsy Center has incorporated the collection of patient-entered validated measures of overall health into routine clinical practice. These include assessments of quality of life (Quality of Life in Epilepsy questionnaire, QOLIE-10), seizure severity (Liverpool Seizure Severity Scale, LSSS), and a screening tool for depressive symptoms (Patient-Health-Questionnaire, PHQ-9) among others. Patients enter their answers in the office waiting room via dedicated electronic tablets prior to every visit. Their responses are reviewed by the treating physician during the outpatient appointment. The physician then answers a set of provider-specific questions pertaining to diagnosis and treatment, approving the incorporation of both physician and patient-entered questionnaires into the patient's electronic medical record and a central electronic database. In this study, we analyze data collected on adult epilepsy patients from 11/08 to 03/10. QOLIE-10 scores are the primary outcome measure. After univariate analyses (t-test and chi-square tests), a multivariate linear regression analysis is performed. Each patient is included only once.

Results: 2185 patients with a confirmed clinical diagnosis of epilepsy, as established by a neurologist with subspecialty training in epilepsy and neurophysiology, were included in this analysis. The questionnaire completion rate was 79%. Mean age was 43.8 years (range 19-98 years median= 42, s.d. 15.7). Fifty four percent were female. The mean QOLIE-10 score in the overall cohort was 21.3 (95% C.I. 20.9-21.6, s.d. of 8.6, range 10-50). Clinical and demographic patient characteristics, and results of the univariate analysis of the QOLIE-10 score predictors are shown in Table 1. After multivariate regression, factors that retain statistical significance include: driving, work status, seizure severity, number of antiepileptic medications, marital status, and depression (R square=0.59, $p<0.0001$). Of all these variables, the two with the most clinically significant implications (a QOLIE-score difference>1-1.5 s.d) were seizure severity (mean QOLIE-10 score 28.5 if LSSS>40 opposed to 18.8 otherwise; effect size 1.8) and depression (mean QOLIE-10 score of 30.7 if PHQ-9 e"10 as opposed to 18.5 otherwise, effect size 3.4). Specifically, although depression and seizure severity were related (51% of patients with severe seizures were depressed as opposed to 17% otherwise; $p<0.0001$), depression remained a major determinant of the quality of life regardless of seizure severity (Fig 1).

Conclusions: Improving the quality of life in patients with epilepsy requires attention to a multitude of factors beyond seizure control, particularly depression, to optimize treatment outcomes.

Overall QOLIE-10 predictors with univariate analyses using the t-test and Chi-square tests:

IMAGE: tables/905760_T1.jpg

QOLIE-10 scores can range from 10 to 50 with higher scores reflecting a poorer quality of life.

IMAGE: images/905760_A.jpg

3.132

FOLLOWING A FIRST UNPROVOKED SEIZURE WHEN IS THE RISK OF A RECCUENCE LOW ENOUGH TO RESTART DRIVING? FURTHER ANALYSIS OF THE MESS STUDY

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Rationale: Driving regulations for people with epilepsy or who have had single seizures differ from country to county and form state to state within the USA. Within the European Union a process is ongoing to harmonise driving regulations across member states. Attempts are being made to make policies risk based and an individual will be allowed to regain their ordinary driving license once their risk of a seizure recurrence in the next 12 months has dropped below 20%. EU guidance suggests that an individual should regain their ordinary driving license once they have gone 6 months seizure free following a first seizure, but there are few data in the public domain that inform this policy.

Methods: The multicentre study of early epilepsy and single seizures (MESS) was a randomized controlled trial that compared the policies of immediate and deferred antiepileptic drug treatment for patients following a single seizure or with 2 or more seizures where the patient and clinician were uncertain about the need to start antiepileptic drug treatment. The analysis presented here is restricted to MESS patients who had had a single seizure and were 16 year or older. We calculated the risk of a seizure in the next 12 months for patients who had gone 3, 6 and 12 months seizure free following their first seizure. Regression modelling was used to investigate how antiepileptic drug treatment and a number of clinical factors influence the risk of seizure recurrence.

Results: 637 of the 1443 patients were included in this analysis. Unadjusted analysis indicate that at six months following a first seizure the risk of a recurrence is significantly below 20% over the next 12 months for patients who start antiepileptic drug treatment, risk 14% (95% CI: 10% to 18%). For patients who do not start treatment the estimate is below 20% but the upper limit of the confidence interval is greater than 20%, risk 18% (95% CI: 13% to 23%). At 12 months the risks are 7% (4% to 11%) and 10% (6% to 15%) respectively. Univariate analyses indicate that the risk of seizure recurrence is higher for patients with a remote symptomatic seizure, neurological deficit, abnormal EEG and a seizure while asleep. Multivariable analyses identify subgroups with an annual recurrence risk significantly greater than 20% after a six month seizure free period.

Conclusions: Following a single seizure this reanalysis of MESS provides estimates of seizure recurrence risks that will inform policy

and guidance about regaining an ordinary driving license. Multivariate analyses identify the characteristics of patients at higher risk of a seizure recurrence. Further policy guidance is needed as to how such data should be utilised. In particular whether a population approach should be taken with a focus upon the unadjusted results or whether attempts should be made to individualise risk. Guidance is also required as to whether the focus should be upon risk estimates only or upon the confidence interval as well. If the latter, direction is needed as to whether a conservative or liberal approach should be taken.

3.133

UTILITY OF IMAGING IN STATUS EPILEPTICUS

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Rationale: Data are limited regarding the yield of central nervous system imaging in newly presenting patients with status epilepticus with no prior history of seizures. Earlier reports have demonstrated up to 49% of brain imaging studies in status epilepticus may be abnormal. In a time where cost-containment needs strong consideration in medical practice, further data are required to determine a yield of abnormalities, particularly those that may alter care.

Methods: The Status Epilepticus Project is an NIH sponsored epidemiology study with a database running continuously from 1989 through the present. 757 consecutive patients were identified presenting as status epilepticus in patients with no prior history of seizures. These patients were analyzed for each, gender, if an abnormality is present, further breakdown into acute structural abnormality such as stroke or hemorrhage, tumor, congenital abnormalities, hydrocephalus, etc.

Results: Imaging was performed acutely in 757 patients. 455 of the 757 (60.1%), either initial CT or MRI, were abnormal. By age, in children one month to one year 15/34 (44.1%) were abnormal. In patients one year to 16 years of age 29/59 (49.2%) were abnormal. In the 16 year to 60 year group 124/161 (77%) were abnormal. In the over 60 year group 161/201 (80.1%) were abnormal.

Conclusions: Patients undergoing acute central nervous system imaging with CT or MRI in status epilepticus patients with no prior history of seizures has a high yield with approximately 60% of studies abnormal. This is highest in the elderly. When the analysis is complete, further conclusions regarding the exact type of abnormality, whether there is a high probability of relationship to the cause of status epilepticus, whether it led to acute intervention will be discussed.

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3.134

RESPONSE TO FIRST ANTIEPILEPTIC DRUG TRIAL PREDICTS HEALTH OUTCOME IN EPILEPSY

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Rationale: Failure to respond to the initially prescribed antiepileptic drug (AED) is a major predictor of poor seizure control. However, no data exists on whether first AED failure also predicts outcome in terms of adverse health status. We performed a case-control study to investigate major adverse health events rates and health assessment ratings in relation to first AED response in patients with newly diagnosed epilepsy.

Methods: Adult patients who were diagnosed and started on AED treatment at the Columbia Comprehensive Epilepsy Center in 2001-2003 and who had at least 5-year follow-up data since diagnosis were identified through chart review. After obtaining written informed consent, eligible patients were interviewed to review data extracted from medical charts and were asked to complete reliable and valid health assessments, including the Quality of Life in Epilepsy (QOLIE)-89, the Adverse Event Profile (AEP), and the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E). We compared rates of major adverse health events (loss of driving privileges, unemployment, divorce/separation, injury, emergency room admission, hospitalization, and death) over 5-7 years after diagnosis between patients who failed the first AED trial (cases) and those who did not (controls). We also evaluated between-group differences in QOLIE-89, AEP, and NDDI-E scores at 5-7 years since diagnosis, adjusting for age and gender.

Results: We enrolled 33 cases and 30 controls. The rates of major adverse health events were similarly high in both groups in the first year after diagnosis (mean ± SD: 2.64 ± 0.99 for cases and 2.50 ± 1.14 for controls), but decreased to a greater extent in controls than in cases thereafter, with a significant between-group difference ($p<0.001$). Two cases died during follow-up, both of sudden unexpected death in epilepsy (SUDEP). Cases had worse QOLIE-89 scores compared to controls ($p=0.02$), while there was no significant between-group difference in AEP and NDDI-E scores.

Conclusions: Patients who fail the first AED trial are at increased risk of experiencing an adverse health outcome. Our findings may support earlier consideration of referral for potential epilepsy surgery.

3.135

THE EFFECT OF SEIZURES ON OUTCOME IN NEONATAL ISCHEMIC STROKE

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Rationale: Seizures frequently occur in neonates with brain injury. Both clinical and subclinical neonatal seizures are reported to correlate with adverse neurodevelopmental outcome. Although neonatal ischemic stroke (NIS) frequently presents with manifested seizures, data are lacking regarding their subsequent evolution and impact on outcome as well as if acute recognition and early treatment of seizures could potentially improve the neurodevelopmental outcome from NIS.

Our objectives were:

1)To determine the frequency of subclinical seizures in acute NIS

2)To evaluate the effect of seizures on radiographic progression of acute NIS

3)To assess the long term neurological outcome in this population (Paediatric Score Outcome Measure [PSOM] and Epilepsy)

Methods: This is a retrospective single center study of neonates prospectively registered in the Canadian Paediatric Ischemic Stroke Registry (CPISR) (Toronto site) with acute NIS (arterial ischemic stroke [AIS] and/or cerebral sinus venous thrombosis [CSVT]) from

January 1999 to December 2006. Inclusion required an electroencephalogram (EEG) performed within 7 days from confirmed NIS diagnosis. Patients were excluded if they were not term (<36 weeks or >46weeks CA) and if EEG trace was not available for review.

Data were abstracted from the CPISR, Hospital Health Records and Neurophysiology Laboratory Database. EEG traces were reviewed by Board Certified Neurophysiologist (MC). Pre and Post EEG neuroimaging data were reviewed blinded by paediatric stroke neurologist (MM). Demographic data, PSOM, progression of ischemic lesions on neuroimaging and epilepsy outcome at last visit were compared between patients with and without seizures on EEG. Statistical analyses were performed using GraphPad 4 software. Significance was set at $p<0.05$ and trend when $p<0.10$.

Results: There were 82 neonates with NIS. 29 were excluded due to incomplete data. Among 53 included patients, 18 (34%) had seizures on EEG recording that were only subclinical in 15 (83.3%) and clinical+subclinical seizures in 3 (16.7%). Demographic data did not differ significantly in patients with (PS) or without (PWOS) seizures. There was no significant difference on stroke progression on neuroimaging follow-up. PSOM scores were significantly worse at follow up between PS (2.8 [95% CI 1.00 - 4.6]) versus PWOS (0.98 [95% CI 0.5 - 1.47]) (p=0.019). Epilepsy at follow up (63.0 months [95% CI 40.9 - 85.1] in PS and 58.2 months [95% CI 48.6 - 67.7] in PWOS, p=0.69) tended to be more frequent in neonates with seizures on EEG (5 out of 18 PS vs. 3 out of 35 PWOS, p=0.089).

Conclusions: In our series, seizures occurred frequently, the majority being subclinical. Neurological outcome was significantly poor in PS.

Close clinical and EEG monitoring to screen for clinical and subclinical seizures is desirable.

Prophylactic treatment with anti-convulsant medications in acute NIS, in order to improve the long term prognosis and potentially diminish the chances of developing epilepsy is worth consideration.

Prospective studies are needed to further address these issues.

IMAGE: images/907261_A.jpg

3.136

INCREASED INCIDENCE OF SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP) WITH LAMOTRIGINE IN ROGALAND COUNTY, NORWAY

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Rationale: Lamotrigine (LTG) has been shown to inhibit the cardiac potassium channel Ikr (Danielsson et al., 2005) and Ikr blocking drugs have been associated with increased risk for the long QT syndrome and sudden cardiac death. Recently we reported four consecutive cases of SUDEP in women with idiopathic epilepsy that were all treated with LTG in monotherapy (Aurlien et al., 2007). An increased risk connected to LTG has, however, never been shown in a clinical study.

Here we present a retrospective population based study on the incidence of SUDEP in Rogaland County, Norway, (375.000 inhabitants) in the ten years period 01.08.1995 - 31.07.2005. The incidence of SUDEP associated with each antiepileptic drug (AED) was estimated.

Methods: The SUDEP victims were identified by review of hospital records and post mortem reports of deceased individuals with a diagnosis of epilepsy and data from the National Causes of Death Registry. The victims were classified according to the definitions of "definite", "probable" and "possible" SUDEP (Tomson et al., 2008). With a prevalence of epilepsy of 0.7 per 1000 (Forsgren L., 2004) the number at risk was estimated to 2612 individuals. Based on the market share in defined daily doses (DDD) the incidence of SUDEP was estimated for each AED. Statistical analysis was performed for AEDs with at least 5 SUDEP victims.

Results: 26 cases (15 females, 11 males) were identified. 16 were definite, 3 were probable and 7 possible SUDEP. The incidence of SUDEP was 1.0 per 1000 patient-years when all 26 cases were included and 0.7 per 1000 patient-years for definite and probable SUDEP.

10 (9 females, 1 male) of the 26 (38.5 %) were treated with LTG; 5 in monotherapy and 5 in polytherapy. 2 /10 were classified as possible SUDEP, both were on polytherapy. 8 of the 19 cases (42 %) classified as definite and probable SUDEP were on LTG.

The incidence of SUDEP for patients treated with LTG (all cases included) was 4.9 per 1000 patient-years compared to 0.7 per 1000 patient-years for patients that were not treated with LTG ($p < 0.001$, odds ratio 7,7 with 95 % confidence interval 3,5 - 16,8).

The incidence of definite and probable SUDEP for patients treated with LTG was 3.9 per 1000 patient-years and 0.46 per 1000 patient-years for patients that were not treated with LTG

($p < 0.001$, odds ratio 8,8 with 95 % confidence interval 3,6 - 21,6).

Among the 26 cases 7 were treated with carbamazepine (CBZ) (4 in monotherapy), and 8 with valproate (VPA) (4 in monotherapy). The SUDEP incidence for CBZ and VPA was not significantly different from the incidence among those not treated with these AEDs. In addition, 3 were treated with phenytoin, 3 with vigabatrin, 3 with oxcarbazepine, 2 with topiramate, 1 with phenobarbital and 1 was untreated.

Conclusions: The incidence of SUDEP in patients treated with LTG was significantly increased compared to other AEDs. The findings may suggest a gender difference with a higher incidence in women. The total incidence of SUDEP in Rogaland County was similar to that of previous population based studies.

3.137

PERINATAL STROKE AND THE RISK OF DEVELOPING EPILEPSY

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Rationale: With an estimated incidence of 1 in 2300 to 5000 births, ischemic stroke is more likely to occur in the perinatal period than at

any time in childhood. Little data are available on the risk and timing of developing epilepsy later in life.

Methods: We retrospectively reviewed data of children with acute and delayed diagnosis of perinatal arterial stroke (PAS) in three tertiary care children's hospitals. Acute presentation of PAS was defined as neurological symptoms occurring before 28 days of life, whether children delayed presentation of PAS appeared neurologically normal in the neonatal period and then presented in infancy with neurological symptoms such as hemiparesis or seizures. Only patients with MRI-documented PAS were included. Over a 5-year period, 42 patients (23 females and 19 males) were identified and charts were queried for demographics, stroke type, clinical presentation, and subsequent development of epilepsy.

Results: All 42 children (100%) had unilateral infarction in the left (28/42, 66%) or right (14/42, 33%) middle cerebral artery territory. 14/42 (33.3%) patients were diagnosed at birth, and 28 (66.6%) had a delayed presentation. Of those 28 babies with delayed presentation, 20 (71.4%) were diagnosed before 12 months of age, and 8 (28.5%) were diagnosed after 1 year of age. The mean age at presentation was 8.5 months (range 0-60 months). Of the 14 babies diagnosed at birth, 8 (57.1%) presented with seizures (2 of whom with focal status epilepticus), 5 (35.7 %) presented with respiratory distress, and one (7.1 %) with congenital palsy of the III cranial nerve. In the 28 patients with delayed presentation, hemiparesis was the most common neurological sign (26/28, 92.8%). In our cohort, 22/42 patients (52.3%) developed epilepsy later in life (mean age at onset 20.7 months, range 3 - 60 months), two (4.7%) had only one febrile seizure and another one (2.3%) had an episode of loss of consciousness, without a clear convulsion. Twelve patients out of 22 developed (54.5%) with focal epilepsy and 9 (40.9%) developed West syndrome. One patient (4.5%) presented with both focal seizures and West syndrome. More than 50% of patients presenting as neonates with seizures (5/8, 62.5%) developed epilepsy later in life, either focal epilepsy (3/5, 60%) or West syndrome (2/5, 40%). Mean age at onset of epilepsy was 22 months (range 6-36 months). In 12 (54.5%) patients epilepsy was easily controlled with AEDs. However, in 10/22 (45.4%) seizures remained uncontrolled despite AEDs polytherapy, and one of these children was successfully treated with surgery.

Conclusions: Seizures are a frequent presenting sign of PAS. In our cohort, more than a half of patients acutely diagnosed presented with neonatal seizures. Childhood epilepsy is a frequent resulting morbidity. Epilepsy occurred later in life in more than 50% of patients, as focal epilepsy or epileptic encephalopathy. Drug-resistance among children with epilepsy following PAS is not uncommon and epilepsy surgery should be considered.

3.138

RHYTHMICAL AND PERIODIC PATTERNS IN ADULTS WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE AND ALTERED MENTAL STATUS

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Rationale: Nonconvulsive status epilepticus (NCSE) and nonconvulsive seizures are a complication of subarachnoid hemorrhage (SAH). Retrospective studies in SAH have shown an association with NCSE and poor outcome. Retrospective studies have shown NCSE in 18% of patients with intracranial hemorrhage. Due to the high incidence of NCSE in patients with SAH and the significant morbidity associated with untreated NCSE, we initiated a prospective observational study of patients admitted to our institution with aneurysmal SAH and depressed consciousness.

Methods: Patients were enrolled from a single tertiary care center. Inclusion criteria were SAH secondary to a ruptured intracranial aneurysm, a Glasgow Coma Scale (GCS) d"8, decrease in GCS of 2 or more points, patients that did not return to baseline within 12 hours of treatment, or witnessed clinical seizure. Prospective data included clinical examination, prior medical history, imaging, angiographic findings, surgical and medical interventions and laboratory values. Outcomes were determined for all patients at the end of the acute hospital stay. Continuous EEG monitoring was performed and scored according to ACNS Subcommittee on Research Terminology for Continuous EEG Monitoring. All data was collected under approved IRB protocols.

Results: Between May 2008 and April 2010, a total of 416 patients were admitted with a SAH associated with a ruptured intracranial aneurysm. Of these, 51 met inclusion criteria and underwent continuous EEG monitoring. 35 patients (69%) had periodic patterns (periodic discharges or rhythmic delta) at some point during monitoring (9 - periodic discharges only, 10 - rhythmic delta only, 16 - both). Only 2 patients (4%) had discrete electrographic seizures during continuous EEG monitoring. In our study population, 12 died (24%) and 28 were severely disabled (modified Rankin Score (mRS) of 5) (55%). With these preliminary results, there was no predictive value between the presence of rhythmical and periodic patterns and outcome (as determined by mRS).

Conclusions: Our prospective study of patients with aneurysmal SAH consisted of patients with a low GCS score at time of presentation, and overall, included a more critically ill population. 69% of patients had rhythmical or periodic patterns on continuous EEG monitoring as defined by the ACNS research terminology. There was no significant correlation between the presence of these patterns and outcome in this high risk population. Further data analysis is underway to determine which other EEG factors, such as the abundance of periodic patterns, may be predictive of outcome and whether treatment had any impact on patient survival. Rhythmical and periodic patterns may not prove to be an independent risk factor for outcome in SAH; however, continuous EEG monitoring will likely continue to be a valuable tool in guiding treatment for critically ill patients.

3.139

SEIZURE OUTCOME IN PATIENTS WITH INTELLECTUAL DISABILITY

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Rationale: To investigate seizure outcome and its predictors in patients with profound intellectual disability (ID) managed in an academic epilepsy center.

Methods: We retrospectively analyzed the data from institutionalized patients with ID and history of seizures seen in the epilepsy clinic over a 5-year period. Pertinent information extracted at the first visit (FV) and last visit (LV) included demographic data, epilepsy syndrome,

seizure frequency, changes in antiepileptic drugs (AEDs) and vagus nerve stimulator (VNS) implants. We classified the seizure frequency into: extremely frequent (e”5/month); frequent (1-4/month); occasional (4-11/year); rare (1-3/year); seizure free (no seizures in 1 year). Based on the change in seizure frequency, we defined the seizure control between FV and LV as: improved; worsened; unchanged seizure free; unchanged seizure frequency. We then defined 2 seizure outcome groups: favorable (i.e., patients who remained seizure free or improved); unfavorable (i.e., patients who continued to have seizures at the same frequency or worsened). For consistency, the patients with rare or occasional seizures at FV who continued to have seizures at the respective frequency at LV were included in the unchanged seizure frequency group. Based on EEG and imaging, we classified the epilepsy syndrome as: focal; multifocal; generalized; unknown.

Results: The patient and seizure outcome data are shown in Table 1. There were 95 patients (51 males), aged 21-74 years, followed for 5-60 months (mean 42). The epilepsy syndrome was defined in 56 patients. Seizure outcome was favorable in 61 (64.2%) and unfavorable in 34 (35.8%) patients. Between FV and LV, the number of AEDs increased (mean 1.78 vs. 2.18), AEDs were completely discontinued in 2 patients, and VNS was implanted in 10 patients. At LV, lamotrigine, levetiracetam and valproate were the most commonly used AEDs in 27-45% of patients while ten other AEDs were used in 1-15% of patients. Univariate analysis (Table 2) showed that the epilepsy syndrome, seizure frequency at FV or VNS implantation were not associated with outcome; however, increase in the number of AEDs, addition of lamotrigine and addition of levetiracetam were significantly associated with unfavorable outcome. Multivariate logistic regression analysis using stepwise variable selection showed that increase in the number of AEDs [odds ratio (OR) 4.70, 95% confidence interval (CI) 1.75-12.61, p=0.002] and addition of lamotrigine in lamotrigine-naïve pts (OR 3.82, 95% CI 1.31-11.13, p=0.014) to be significantly associated with unfavorable outcome.

Conclusions: Nearly two-thirds of patients with profound ID and epilepsy achieved favorable seizure outcome. The epilepsy syndrome, seizure frequency at first visit and VNS did not predict outcome. However, the need for increased number of AEDs to control seizures, and the addition of broad-spectrum AEDs, particularly lamotrigine, predicted unfavorable outcome. These results highlight the refractory nature of epilepsy and the challenges of management in this population.

Acknowledgement: The study was supported in part by a grant from the Commonwealth of Kentucky.

Table 1. Patient characteristics and seizure outcome

IMAGE: tables/900211_T1.jpg

AEDs, antiepileptic drugs; VNS, vagus nerve stimulator.

Table 2. Univariate analysis of seizure outcome in 95 patients

IMAGE: tables/900211_T2.jpg

[a]Chi-square test; [b]Fisher’s exact test.

AEDs, antiepileptic drugs; FV, first visit; LV, last visit; VNS, vagus nerve stimulator.

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THE EFFECT OF LEAD TIME TO TREATMENT AND OF AGE OF ONSET ON DEVELOPMENTAL OUTCOME IN INFANTILE SPASMS: EVIDENCE FROM THE UNITED KINGDOM INFANTILE SPASMS STUDY (UKISS)

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Rationale: Infantile spasms is a severe infantile seizure disorder which is difficult to treat and has a high morbidity. Several factors affect developmental outcome the most important of which are the underlying aetiology of the spasms. Treatment affects outcome and both the age at onset of spasms and the time between onset of spasms and treatment, that we call lead time to treatment, have also been suggested as important. We examined this in the United Kingdom Infantile Spasms Study.

Methods: Developmental follow up of infants in UKISS was performed using the Vineland Adaptive Behaviour Scales at 4 years of age. Information on date of onset or age of onset of spasms was obtained prospectively and lead-time to treatment was categorised post hoc into groups: 7 days or less; 8 - 14 days; 15 days - 1 month; 1 - 2 months, greater than 2 months or not known. No hypothesis was investigated for any specific lead time or age of onset.

Results: 77 infants were assessed at 4 years. Age of onset of spasms in this group ranged from less than one month to 10 months (mean 5.2 months, standard deviation 2.1 months) and lead time to treatment was 7 days or less for 11, 8 - 14 days for 16; 15 days - 1 month for 8; 1 - 2 months for 15, greater than 2 months for 21 and not known for 6. The effects of lead-time to treatment, age of onset of spasms, aetiology and treatment on developmental outcome were investigated using multiple linear regression. Age of onset of spasms (regression coefficient 3.1, p=0.014) and lead-time to treatment (regression coefficient -3.9, p=0.03) were both significantly associated with development. There was also a significant interaction between treatment and aetiology with regards to developmental outcome (regression coefficient 29.9, p=0.004).

Conclusions: In infantile spasms, later age at onset of spasms is associated with better developmental outcome suggesting that younger infants may be more susceptible to damage from the presence of an epileptic encephalopathy. Increasing lead time to treatment is associated with worse developmental progress suggesting that prompt diagnosis and treatment of infantile spasms may help prevent developmental delay.

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THE DURATION OF THE NEGATIVE MYOCLONIAS IS A MAIN REASON FOR THE PROGRESSION IN LOCOMOTORY DISABILITY IN PATIENTS SUFFERING FROM UNVERRICHT-LUNDBORG DISEASE

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Rationale: Most patients with Unverricht-Lundborg disease or EPM1 develop during the course of the disease a locomotory disability. Our hypothesis was that negative myoclonias are the main reason for the locomotor disability and investigated their progression.

Methods: In 15 patients with EPM1, all proven by mutation of the CSTB gene, ictal polygraphic video-EEG-recordings (16 channel EEG, 8 channel surface EMG) were done in freely moving or standing patients. At least two recordings were performed in 8 EPM1 patients with a mean intervall of 12.8 years between them. Criterion for the duration of the negative myoclonias was the duration of the silent periods in the EMG. In a first approach the silent periods of the 8 patients with 2 polygraphic recordings were compared at the different time points (T1, T2). In a second approach all 15 patients were cross-sectional grouped in capable of walking without aid, with aid and in need of a wheelchair.

Results: All 15 patients had documented negative myoclonias in their polygraphic recordings when standing or walking. A direct confirmation for a significant extension of the duration of the silent periods over the years from 100 (SD 19.1) ms ad T1 to 128 (SD 26.6) ms at T2 was found in 7 of the 8 patients.

In the second approach patients with no disturbance in walking had a mean duration of 97.3 (SD 16.5) ms, patients who were handicapped in walking had a mean duration of 106.7 (SD 16) ms, patients who were bound to a wheelchair had a mean duration of 139 (SD 23.6) ms. The increment in frequency of the negative myoclonias was not quantitativly investigated. In the wheelchair patients, the negative myoclonus was, while walking more continous and tremolous. In contrast the patients with no disturbances, negative myoclous more seldom

Conclusions: We have shown, using simultaneous EEG/EMG recordings in freely moving patients, that the locomotor disability is in fact mainly due to negative myoclonus in voluntary innervated muscles. One reason for the progression of the disability is the lengthening of the duration in the measurable silent periods, as measure for the duration of the negative myoclonias

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HOW DO NEUROLOGISTS USE EEGS WHEN WITHDRAWING AEDS IN SEIZURE-FREE PATIENTS? RESULTS OF AN INTERNATIONAL INTERNET-BASED QUESTIONNAIRE

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Rationale: We wanted to determine how much variability there is in neurologists' use of EEG when discontinuing anti-epileptic drugs (AEDs) in patients with epilepsy who are seizure-free.

Methods: An Internet-based questionnaire was sent to adult and paediatric neurologists with an interest in epilepsy in New Zealand, Australia, Pakistan, Malaysia, Great Britain, Italy, Belgium and Canada. The questionnaire addressed physician's use of EEG in deciding whether to discontinue AEDs in seizure-free patients. The questionnaire contained 7 common clinical scenarios allowing open ended and closed responses.

We sought to determine:

1) in what circumstances neurologists obtain an EEG when considering withdrawal of AEDs in patients who are seizure-free;

2) how the results of the EEG influence the neurologist's decision;

3) what other clinical factors affect AED withdrawal;

4) the rate of AED withdrawal.

Results: Neurologists from all 8 countries responded. There was substantial variability in the use of EEG, both between and within countries. Of the initial 100 respondents, 45% always obtain an EEG before withdrawing an AED in a seizure-free patient taking a single drug, 37% sometimes obtain an EEG, and approximately 18% never do so. Approximately 30% of doctors report that they never obtain an EEG when discontinuing one of several AEDs. A routine 20-40 minute recording is most widely used. The most important factors determining whether an EEG is obtained are the epilepsy syndrome, the seizure type, the presence of epileptiform discharges in an earlier EEG, and uncertainty regarding the original diagnosis. In only 3 of the 7 scenarios did more than half the epileptologists agree on the approach. Approximately 2/3 would be guided by the EEG when considering withdrawal of AEDs in a child with absence epilepsy. In the other 2 scenarios where more than half agreed on the management, the majority of neurologists stated they would advise the patient not to discontinue the AED, regardless of what the EEG showed. Fewer than 20% of neurologists would be guided by an EEG in other clinical scenarios. Most neurologists withdraw AEDs over 3 to 6 months, but significant numbers withdraw more rapidly or more slowly.

Conclusions: There is considerable variability in the use of EEG when withdrawing AEDs in seizure-free patients. There was little agreement regarding its usefulness in several common clinical scenarios. A multicentre trial should be considered to guide rational decision-making in this common clinical setting.

3.143

USE OF A NEW DISABILITY SCALE-SERDAS IN EPILEPSY PATIENTS

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Rationale: In order to evaluate various aspects of seizure impact on epilepsy patients there are several useful scales but none measure

disability.Since patients can have episodic disability from seizures and from medication side effects we designed a new scale for measuring dysfunction related to seizures and seizure therapy for assessing epilepsy patients. Due to the episodic nature and other clinical similarities between migraines and seizures we developed a new scale SERDAS (seizure related disability assessment scale) based on the validated migraine disability scale MIDAS (Migraine Disability Assessment Scale). To test the design, we compared the results on the SERDAS in two epilepsy populations, one of which is severely disabled (patients admitted to an epilepsy monitoring unit for presurgical evaluation or classification) and the other of which is less severely disabled (patients from an outpatient epilepsy clinic.)

Methods: SERDAS is a six-item questionnaire designed to measure seizure severity based on dysfunction related to number of events, as well as to medication side effects and other seizure-related dysfunction. The last question will not contribute to the total points on the scale, but will give the clinician an idea of patient dysfunction perception.

This was a prospective study of 80 patients with epilepsy. 35 patients admitted to Epilepsy monitoring unit (EMU) either for pre-surgical work up or classification of the epilepsy syndrome and 45 patients followed at epilepsy clinic were included in the study. The following information was obtained; Age, gender, age of onset, number of current antiepileptic drugs (AEDs) on and number of past AEDs ,epilepsy syndrome, number of seizures past month, presence of generalized tonic clonic seizures

Results: The average age was 34.4 in EMU group, 36.5 in outpatient group. The most common epilepsy syndrome was localization related epilepsy. The groups were similar in age, number of AEDs, past AEDs, percent with localization related epilepsy, days with seizures and self disability report. We found that there was no significant difference between the two groups (15.8 compared to 10.9) $p<0.55$. Self disability report was slightly higher in the EMU subjects $p<0.52$.

Conclusions: There is a clinical need for a scale to evaluate the intermittent disability that epilepsy patients suffer when they have seizures or medication side effects . We hypothesized that EMU patients would be more disabled than outpatients and tested the SERDAS scale in the two groups. Our results show that the groups were similar in age, number of AEDs, past AEDs, percent with localization related epilepsy, days with seizures, self disability, and SERDAS scores. We found that there was no significant difference between the SERDAS scores for two groups, possibly because the two groups had such similar characteristics. In the future we will pilot the SERDAS again, but we will use groups that are more clearly distinct clinically.

Demographics and Clinical Features of the Two Groups

IMAGE: tables/906979_T1.jpg

Appendix 1 SERDAS Scale

IMAGE: tables/906979_T2.jpg

SERDAS (Seizure related disability assessment scale)

This is a short questionnaire that will give your doctor information about how much your seizures are interfering with your ability to function on a day-to-day basis. Please read the instructions carefully before answering the questions.

Instructions:

If you are completely unable to work or go to school do not include this in days missed. Only count days missed if you are currently working and/or going to school, and have to miss a day.

Please count sleepiness/headache/confusion after a seizure, (or anything that happened after a seizure which disabled you) in your time estimates. If you had to go to an ER, count this time also.

Do not count any dysfunction that you experience that was not directly related to a seizure or side effect of medication (For example, chronic memory problems).

Please answer the following questions:

1. How many days in the last month have you not been able to function at work/home/school activities for > 50% of the day due to seizures or seizure-related problems?

_____

2. How many days in the last month have you not been able to function at work/home/school activities for > 50% of the day due to medication side effects?

_____

3. How many days in the last month was your productivity at work/home/school activities reduced by 25-50% due to seizures or seizure-related problems?

_____

4. How many days in the last month was your productivity at work/home/school activities reduced by 25-50% due to medication side effects?

_____

5. On how many days in the last month did you miss a family, social or non-work activity because of your seizures or seizure-related dysfunction?

_____

6. On how many days in the last month did you miss family, social or non-work activities because of medication side effects?

_____

On the scale below, mark down how disabled you think you were over the past month as a result of your seizures, seizure-related dysfunction or seizure medication side

Effects, with 0 being no disability, and 10 being extremely severe disability.

No Disability 0—1—2—3—4—5—6—7—8—9—10 Extremely severe disability

3.144

ABNORMAL MRI IS A PREDICTOR OF POOR OUTCOME IN FOCAL EPILEPSY

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Rationale: The aim of the study was to analyze if epileptogenic lesions found on brain MRI studies are predictive of bad response to the pharmacological treatment in epilepsy patients.

Methods: We selected epilepsy patients who had been a MRI done. According to the response of the pharmacological treatment they were classified into 2 groups: Drug Resistant and Non-Drug Resistant. We analyzed the variables: age, age at onset (AO), time of the evolution (TE), localization of the epileptogenic zone and the presence of an epileptogenic lesion on the MRI.

Results: Three hundred and twenty three patients with focal epilepsy were included. There were differences in AO less in Drug Resistant patients and TE less in Non-Drug Resistant. Patients with focal epilepsy and an abnormal MRI were 2.3 times more likely to be drug-resistant than patients with a normal MRI. These three variables were considered independent risk factors for intractability.

Conclusions: A MRI showing an epileptogenic lesion is a predictor of poor outcome in patients with focal epilepsy.

3.145

NEUROPATHOLOGICAL STUDY OF MEDICALLY INTRACTABLE MESIAL TEMPORAL LOBE EPILEPSY (MTLE): HISTOLOGICAL & MRI CLASSIFICATION OF HIPPOCAMPAL SCLEROSIS AND ITS CLINICAL RELEVANCE

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Rationale: In human temporal lobe epilepsy, hippocampal sclerosis is the typical features in both MRI and neuropathological examinations of resected specimen. In this paper, the precise correlation of MRI and neuropathological findings of hippocampus will be presented. In addition to that, postoperative seizure control in terms of MRI and neuropathological findings will be analyzed.

Methods: Neuropathological findings of selective amygdalohippocampectomy with or without temporal lobectomy specimen surgically resected from 41 patients with medically intractable mesial temporal lobe epilepsy have been analyzed. Neuroradiological analysis has been also performed in 50 patients including these 41 patients. The correlation of MRI and neuropathological findings will be presented.

Results: In the amygdala, diffuse gliosis without neuronal loss was observed in most cases (86.1%), while neuronal loss was observed in only one case. The pattern of hippocampal sclerosis (HS) was classified histologically into the following 4 categories according to the severity of neuronal loss and gliosis in each hippocampal subfield and dentate gyrus: HS type 1 (n=21, 61.0%); CA1 > CA3, CA4 and polymorphic layer of dentate gyrus (PLDG) > (CA2), HS type 2 (n=1, 2.4%); CA1 sclerosis, HS type 3 (n=7, 17.1%); PLDG, CA4 > CA3 > CA1, (CA2), including so called 'end folium sclerosis', and No HS (n=8, 19.5%). HS subtypes didn't correlate with duration of illness, age of onset and operation, suggesting distinct subtypes of HS. HS type 1 seemed to correlate with better postoperative seizure outcome than other subtypes; however, surgical procedure also seemed to be an important factor affecting the seizure outcome regardless of HS subtypes. In 5o patients, typical hippocampal scrclosis has been found in 31, and postoperative seizure control was as follows, Engel's Class I 23, II 3,III 5, and cure rate (I+II) was 83.8%. In 7 patients,there was no hippocampal sclerosis, and seizure control was Class I 4, II 2,III 1, and cure rate was 85.7%. In 4 patients only hiper intensity was found, and seizure control was class I 3, III 1, cure rate was 75%. Only small hippocampus comparing to contralateral side was found in eight patinets, and seizure control was class I 1, II 2,III 4, IV, and cure rate was 33.3%.

Conclusions: MRI findings correlated well with postoperative seizure control. Typical hippocampal sclerosis, no hippocampal sclerosis, and only hippocampal high intensity cases have shown relatively good seizure control comparing those showing only small hippocamal volume. Further analyses of precise correlation of neuropathological and MRI findings will be studied and presented.

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SEIZURES AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN

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Rationale: Neurological complications are reported in 11 to 70% of recipients of hematopoietic stem cell transplantation (HSCT) in children, with seizures as the most common symptom. The authors here describe the clinical manifestations and risk factors for seizures occurring after HSCT in children, and compare the 3-year survival rates of those who experience such seizures and those who do not.

Methods: A total of 197 pediatric patients (113 male, 84 female) received HSCT at the HSCT center, St. Mary's Hospital, the Catholic University of Korea, from August, 2001 to August, 2005. Of these patients, 28 patients (21 male, 7 female) experienced seizures after HSCT. Patient population was divided into 2 groups according to age at the time of HSCT : (1) < 5 years old, and (2) e" 5 years old. The time of seizure onset was divided into 3 periods: (1) less than 1 month after HSCT : the period of engraftment, and (2) between 1-3 months after HSCT : the period of acute graft versus host disease, (3) 3 months after HSCT : the period of chronic graft versus host disease.

Patient variables such as, age, sex, method of HSCT, use of total body irradiation, use of busulfan, the stage of acute graft versus host disease (aGVHD), the malignant or non-malignant nature of the patient's

underlying disease, were analyzed to decide upon risk factors for seizures after HSCT. The 3-year survival rate of patients experiencing seizures after HSCT was compared to that of patients who did not experience seizures.

Results: The overall incidence of seizures developing after HSCT was 14.2%, with boys reporting a higher incidence than girls. No significant difference was found with regards to onset and type of seizure. Abnormal neuroimaging findings were noted in 20 patients (76.9%), with posterior reversible leukoencephalopathy syndrome being the most common finding. EEG abnormalities were noted in 21 patients (91.3%); cortical dysfunction was the most prevalent EEG finding. Amongst the possible risk factors for seizures, the age of the patient and the grade of aGVHD were statistically significant. Patients age of 5 years or older showed a 4.2 times greater incidence of seizures (P=0.025) than those younger. Also, patients with grade 2-4 acute GVHD showed a 2.77 times greater incidence of seizures (P=0.034) than those with grade 0-1 aGVHD. The 3-year survival rate of patients experiencing seizures was 37±9%, compared to 68±3% for those who did not experience seizures (P<0.001).

Conclusions: (1) 14.2% of pediatric patients who received HSCT experienced seizures after transplantation.

(2) Factors predicting seizures after HSCT: 1) Patient age : e" 5 years old, 2) GVHD of grade 2 or above

(3) The 3-year survival of patients experiencing seizures after transplantation was significantly lower than patients who did not undergo seizures.

(4) Early investigations and prompt treatments are required for pediatric patients experiencing seizures after HSCT as such seizures seem to have a direct linkage with the long term prognosis of the patient.

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NEW ONSET CRITICAL SEIZURES IN THE ELDERLY: EXPERIENCE FROM A TERTIARY CARE CENTRE FROM SOUTH INDIA

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Rationale: Status epilepticus (SE) constitutes an important neurologic emergency among the elderly and focused study in this subgroup of patients who manifested with critical seizures i.e. SE and cluster of seizures are far and few. To evaluate the frequency, therapeutic response and predictors of critical presentation of seizures among the elderly

Methods: Elderly patients with epilepsy >60 years (n=201; age: 68.0,SD:7.5) were prospectively recruited. Sixty four (32%)patients who presented with cluster attacks and/or status

epilepticus(SE)were considered to have critical seizures. All underwent EEG and CT scan.

Results: The mean duration of critical seizures was 14.9 ± 53.7 hours. Cluster attacks were observed in 53 (26.4%) and SE in 34 (17%). The types of SE were generalized convulsive (23), epilepsia partialis continua (8), non-convulsive (2) and myoclonic (1). The types of epilepsy syndrome included acute symptomatic - 37 (57.8%), cryptogenic - 15 (23.4%), and remote symptomatic - 12 (18.8%). Interictal EEG was abnormal in 79.7% of patients with critical presentation vs. 53.3% of patients without critical presentation. Epileptiform activity was observed in 46.9% of patients with critical presentation vs. 27.0% without critical presentation (p=0.001). The neuroimaging differences in two groups were absence of white-matter changes on CT in those with vs. without critical presentation (28.1% vs. 41.6%, p=0.06). The markers for critical seizures were - acute symptomatic seizures, simple partial seizures, and higher number of seizures, lower GCS score, and absence of white-matter changes on CT. After multivariate analysis, lower GCS score (p=0.01; OR = 0.82), and more number of seizures (p=0.03; OR = 1.03) significantly predicted the critical presentation. Seizures were controlled with 2 AEDs in 70.6%.

Conclusions: Critical presentation of seizures was common (32%) among elderly. Early and aggressive treatment is effective in the majority.

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POSTOPERATIVE INTERICTAL EPILEPTIFORM DISCHARGE WITHIN ONE MONTH IS ASSOCIATED WITH SEIZURE RECURRENCE AFTER ANTERIOR TEMPORAL LOBECTOMY

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Rationale: To investigate the relationship between seizure outcomes and interictal epileptiform discharges (IEDs) within one month after anterior temporal lobectomy (ATL).

Methods: Data were reviewed from patients who had undergone ATL for nonlesional mesial temporal epilepsy between 1987 and 2007. We included patients who had preoperative MRI, preoperative IQ test and seizure outcomes that were followed up for at least two years. Postoperative EEG within 30 days and other preoperative variables were analyzed to examine the significant factors that determine freedom from disabling seizures at two, five and 10 years after ATL and the risk factors for recurrence.

Results: In total, 202 (107 left ATL, 95 right ATL) patients were enrolled in this study. Postoperative EEG was done at an average of 11 days after surgery. IEDs were noted in 29 patients (22.3%) of the 130 patients without seizure for two years after ATL compared to 31 patients (43.1%) of the 72 patients with recurrent seizures (p=0.002). Postoperaive IED remained an independent predictive factor for seizure outcomes by logistic regression (adjusted OR 2.38, 95% CI 1.18-4.81, p=0.016, 2 years postoperatively; adjusted OR 2.22, 95% CI 1.03-4.82, p=0.043, 5 years postoperatively) and Cox hazard regression analysis (adjusted HR 1.76, 95% CI 1.18-2.62, p=0.006) after controlling other predicting factors (unilateral hippocampal atrophy, history of febrile seizure and IQ tests).

Conclusions: In this study, IEDs on the EEG obtained soon after surgery were associated with postoperative seizure recurrence and these results can be used in the risk assessment of seizure recurrence after ATL.

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PROGRESSIVE DETERIORATION OF HEART RATE VARIABILITY PRIOR TO SUDEP

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Rationale: Poorly controlled epilepsy is associated with higher mortality rates than the general population. A significant number of these deaths are due to Sudden Unexplained Death in Epilepsy (SUDEP). The mechanisms of SUDEP are not completely understood, but may be linked to defective autonomic control of the heart and impaired Heart Rate Variability (HRV). There is growing evidence that vagus-mediated (parasympathetic) components of HRV may be biomarkers of SUDEP. We report a patient who died of autopsy-confirmed SUDEP who underwent serial monitoring of HRV prior to death. To our knowledge, this is the first documented case of SUDEP in whom long-term serial HRV measures were performed prior to death.

Methods: A 33-year-old male with a 15 year history of intractable bi-temporal epilepsy was monitored as part of a longitudinal clinical trial. Three HRV measures were taken at four-month intervals, with the final measure taken five weeks prior to his expiration. The HRV values were determined using 1-hour Holter electrocardiography (Phillips Zymed). Artifacts were removed and automated software (Kubios HRV, Kuopio, Finland) was used to compute time-dependent, frequency-dependent, and non-linear measures of HRV.

Results: Key measures of HRV progressively declined during the seven months before death. Measures of HRV taken at the final visit, including SDNN (42.4 ms, decreased 43.5% from baseline), and SDANN (18.2 ms, decreased 42.4%) were substantially lower than his baseline and published norms. (Evrengül 2005) HRV measures specifically associated with vagus-mediated parasympathetic control were particularly depressed, including RMSSD (20.4 ms, decreased 35.9%), pNN50 (2.9%, decreased 72.9%), and HF power (102 ms^2, decreased 71.1%).

Conclusions: A progressive deterioration of HRV occurred prior to the patient's death, especially measures associated with vagus control of the heart (RMSSD, pNN50, and HF power). This supports growing evidence that HRV may be a premorbid biomarker of SUDEP. Serial measures of HRV may help to identify subjects at risk for SUDEP.

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DOES SEIZURE RELATED HEAD INJURY INFLUENCE HEALTH RELATED QUALITY OF LIFE IN PEOPLE WITH EPILEPSY?

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Rationale: Seizure related head injury (SRHI) is an under-recognized condition that is frequently experienced by people with epilepsy (PWE) (Beghi, 2002; Friedman, 2010). The purpose of this study is to investigate the potential impact of SRHI on health related quality of life (HRQOL) among PWE receiving care in a tertiary epilepsy center.

Methods: Since February of 2008, the Baylor Comprehensive Epilepsy Center (BCEC) has been systematically assessing for seizure related injury during initial and routine follow-up visits, specifically questioning for a history of injury since their last visit. This has led to a database of over 300 patients, with 74 patients experiencing recurrent injuries, the majority of which (74%) were SRHI (Friedman, 2010). Consecutive adult PWE receiving care at BCEC were recruited for the study. After obtaining informed consent, patients were administered the QOLIE-31, a standardized questionnaire used to measure HRQOL. Because depression had consistently been associated with poor QOL among PWE (Boylan, 2004), the NDDI-E was administered to screen for depression. Clinical variables measured included age, gender, epilepsy classification, epilepsy duration, past and recurrent SRHI, seizure frequency, and seizure type. Injury severity classification was made and based on a previously published scale (Friedman, 2010). The associations between clinical variables and QOL were determined using a generalized linear model with the total QOLIE-31 score representing the dependent variable.

Results: A total of 129 patients participated in the study (mean age 38 years, 52% male, median seizure frequency 1/month, median epilepsy duration 15 years). Thirty seven (29%) screened positive for depression, 30 (23%) had a history of remote SRHI with no injury sustained during the two year study period, and 35 (27%) experienced recurrent SRHI during the past two years, with the most recent injury occurring within 5 months prior to completion of the questionnaires (median = 2 months following injury). Most (81%) SRHI were classified as mild and others as moderate. On univariate analysis, age, seizure frequency, depression, past SRHI and recurrent SRHI were all associated with poorer QOL scores on the QOLIE-31. However, on multiple regression analyses, only depression ($p < 0.001$) and recurrent SRHI ($p = 0.008$) remained as independent predictors.

Conclusions: Depression was a strong predictor for HRQOL in PWE and is consistent with other recent observations. These data also demonstrate that recurrent SRHI independently impacts HRQOL. The potential long term clinical effects of SRHI in PWE require further study.

IMAGE: images/886847_A.jpg

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A CASE OF NON-HERPETIC ACUTE LIMBIC ENCEPHALITIS WITH SEVERE PSYCHIATRIC SYMPTOMS

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Rationale: Non-herpetic acute limbic encephalitis (NHALE) is a cause-unknown, inflammatory disease entity that affects the limbic system restrictedly. We report here a case of NHALE with transient severe mental disorder. Although the patient had severe psychiatric symptoms, he could recover with mild intelligence retardation.

Methods: A fourteen-year old boy developed a complaint of right-upper-limb paralyses, dysarthria and headache. These symptoms improved within several hours. However, psychiatric symptoms such as anxiety and fretfulness, and fever were developed. Brain magnetic resonance (MRI) showed a hyperintensity lesion in the left parahippocampal gyrus on fluid-attenuated inversion recovery (FLAIR) images. EEG showed high-voltage slow wave in bilateral frontal pole. Analysis of the cerebrospinal fluid (CSF) showed slight increase of leukocyte count. An anti-GluRdelta2 IgM antibody was positive in blood. We diagnosed him NHALE.

Results: He was administered acyclovir (10mg/kg/day), steroid pulse therapy (500mg/kg/day, 3 days), followed by high dose gamma globulin therapy (0.4g/kg/day, 5 days). After that his fever mildly decreased. As his psychiatric symptoms (character disorder, visual and auditory hallucination) were getting worse, he needed to be sedated. He transferred to our hospital because he needed to be hospitalized in the psychiatric ward. He was treated with high dose gamma globulin therapy (0.4g/kg/day, 5 days) followed by steroid pulse therapy (1000mg/kg/day, 3 days). Afterwards, his psychiatric symptoms improved mildly. After he was discharged, he was with mild intelligence retardation as an aftereffect, and yet he was able to pass the entrance examination for high school.

Conclusions: We treated a patient with NHALE. He recovered from severe psychiatric symptoms within 2 months. We report this case with a few similar cases in the past literatures.

3.152

FAVORABLE OUTCOME IN NEAR SUDEP FOLLOWED BY REFRACTORY STATUS EPILEPTICUS

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Rationale: The mechanism of SUDEP is unclear; cardiac and pulmonary mechanisms have been implicated. Ictal asystole is a well described event occurring with temporal lobe seizures. We describe our experience with near death in temporal lobe seizures and the neurologic and cardiac prognosis.

Methods: A forty year old female was monitored in the intensive care unit when she developed ictal bradycardia, asystole requiring resuscitation, and prolonged status epilepticus.

Results: A forty year old female with hypertension presented with a week long history of episodic chest pain, clamminess, and pre-syncope. She experienced a “burning” odor and a “funny feeling” with these episodes. She was found in a confusional state by family and taken to a local hospital. She had multiple generalized convulsions associated with bradycardia. She was loaded with phenytoin and transferred to our institution. During transfer the patient had a staring episode, after which she became asystolic and subsequently had a generalized convulsion. She was unresponsive and required atropine, after which she recovered. Upon arrival at our institution, she had an unremarkable neurologic and cardiac examination, a normal EKG, and a normal EEG.

She had another asystolic episode that required CPR for one minute and atropine injection. About thirty minutes after the return of spontaneous circulation, her neurologic exam was normal except for mild confusion. A temporary transvenous pacemaker was placed. She remained confused, and continuous EEG monitoring was initiated. Multiple seizures were recorded, originating independently from both temporal lobes. Both right and left sided temporal seizures led to pacemaker activation. She was treated with lorazepam and levetiracetam. She was intubated and started on a continuous infusion of propofol.

She had multiple seizures per hour over the next two days, requiring the addition of midazolam and oxcarbazepine. Lumbar puncture and MRI were unremarkable. The pacemaker was deactivated for MRI, and afterward the patient had recurrent seizures but no recurrent cardiac events. Burst-suppression was achieved with the addition of pentobarbital. Over the next three weeks, attempts to wean any of the continuous infusions were unsuccessful, until topiramate, lacosamide, and felbamate were added. Seizures did not recur after the fortieth day of hospitalization.

Due to complications with urinary and pulmonary infections, a permanent pacemaker was not placed. Eventually the patient awoke, was weaned from the ventilator, and underwent intense rehabilitation. She currently lives at home with her family and is not able to work due to cognitive dysfunction. One year later, the patient and her family continue to decline pacemaker placement. Currently she does have one seizure every three months, without cardiac events, and she is maintained on phenytoin, phenobarbital, levetiracetam, and felbamate.

Conclusions: Ictal asystole associated with temporal lobe seizures may play a role in SUDEP. The natural history, recurrence, and prognosis of ictal asystole remain unclear and require further study.

3.153

CENTRAL ICTAL APNEA AS A RISK FACTOR FOR SUBSEQUENT SUDEP

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Rationale: Ictal apnea and hypoxia can be seen in around 1/3 of patients with intractable focal epilepsy and has been implicated as a mechanism of sudden unexpected death in epilepsy (SUDEP). However, an epidemiologic link between ictal hypoxia and subsequent SUDEP has not been established. We wish to report a patient with new-onset temporal lobe epilepsy and severe central apnea and hypoxia during video EEG monitoring who subsequently passed away at home from autopsy confirmed SUDEP.

Methods: 30-year old right handed female with no prior medical history and no known epilepsy risk factors who presented in status epilepticus to an outside hospital with seizures arising from both temporal lobes, > 100 within the first 4 days. An extensive workup yielded an elevated thyroid-peroxidase antibodies of 354.4 and lymphocytic pleocytosis on CSF. She was in the intensive care unit for several weeks and discharged on carbamazepine and phenobarbital and a short course of steroids. She continued to have weekly complex partial seizures often with noticeable pallor. Nine months after disease onset, she was found dead by family members in the morning in prone position. The family was not alerted by the auditory alarm system in her room or by sleeping next room with open doors.

Results: Video EEG monitoring 4 months before her death was reviewed. She had been on long term video EEG with concurrent monitoring of EKG and respiratory parameters (chest and abdominal wall excursion, airflow, end-tidal CO2, O2 saturation, see figure 1). Her interictal EEG was noteworthy for intermittent generalized slowing and bitemporal sharp waves. Several seizures while monitored arising from the left temporal lobe associated with ictal apnea and oxygen desaturation below 70% were recorded, associated with staring and subtle bilateral tonic movements.

Figure 1: EEG seizure onset precedes the clinical onset by 50 seconds. A broadly distributed left hemispheric sharp wave maximum temporal followed by a low amplitude rhythmical activity is seen at onset (see insert). The ictal pattern spreads to the contralateral temporal lobe approximately 1 minute after clinical seizure onset. Patient’s baseline EKG shows a normal sinus rhythm at 60 beats per minutes (bpm) during sleep which doubles during the event. Patient’s baseline O2 saturation was measured at 93% and her ETCO2 was 46-47 mm Hg. Approximately 40 seconds after EEG seizure onset, she was noted to

have central apnea with absent chest and abdominal excursion for over 1 minute associated with a maximum O2 desaturation of 68 %.

Conclusions: We present a patient with temporal lobe epilepsy associated with central ictal apnea and severe oxygen desaturation who subsequently died of SUDEP. The case strongly suggests that ictal apnea may be a risk factor for SUDEP. It also demonstrates that standard video EEG monitoring with EKG is insufficient to detect ictal apnea. Desaturation and SUDEP can occur in partial seizures even without noticeable convulsive activity. Oxygen monitoring and hypoxia triggered alarm systems may improve the safety of patients during seizure recording and if technically feasible also at home.

IMAGE: images/907215_A.jpg

3.154

CLINICAL CHARACTERISTICS AND OUTCOMES OF NEONATAL SEIZURES IN A SINGLE CENTER

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Rationale: Neonatal seizure is the most common neurologic manifestations in neonates and it could be an important clinical sign of potential brain disorders. The incidence is reported as 1 to 14 per 1,000 live births. It increases the risk of neurodevelopmental impairment, but sometimes it could be difficult to diagnose neonatal seizure due to its variable and subtle clinical features. Early detection of seizure and proper treatment of underlying etiologies as well as seizure itself is very important. The aim of this study is to review the clinical characteristics of neonatal seizures and find the prognostic factors such as etiologies and brain imaging studies. This study could be a valuable data to understand and manage the neonatal seizures.

Methods: Twenty-one neonates with clinically identified seizures within one month old who admitted to Dankook University Hospital from July 2007 to June 2009 were included in this study. The medical records including informations about baseline characteristics, etiologies, seizure types, brain imaging such as sonography or MRI, sleep EEGs as well as medications and clinical outcomes were reviewed, reterospectively.

Results: Among 21 neonates, 18 (85.7%) were term neonates and 3 (14.3%) were preterm babies. Males (14, 66.7%) were predominant. There were no difference in the delivery patterns (vaginal delivery, 47.6%). The main cause was hypoxic-ischemic encephalopathy (HIE, 7, 33.3%) and there were many other casues including stroke (3, 14.3%), metabolic disturbances such as hypoglycemia or severe hypernatremic dehydration (3, 14.3%), brain anomaly such as partial callosal dysgenesis or left hemimegalencephaly (2, 9.5%), and pyridoxine dependent seizure (1, 4.8%). No more seizure was developed in 4 neonates without medications. Other 17 neonates were treated with anticonvulsants (phenobarbital only in 11, phenobarbital and phenytoin in 2, and multiple drug combinations in 4). One neonate expired due to refractory status epilepticus. Moderate to severe HIE had more grave outcomes.

Conclusions: In this study, one third of neonatal seizures were caused by HIE, and moderate to severe HIE had more grave outcomes. In addition, neonatal seizure was a very important clinical sign of a variable underlying etiologies such as stroke, metabolic insults or congenital brain anomaly, therefore, intensive workup and prompt management should be considered for better outcomes.

3.155

OUTCOME OF PATIENTS WITH PLEDS DURING CONTINUOUS EEG MONITORING

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Rationale: Periodic lateralized epileptiform discharges (PLEDs) are seen with a variety of neurological conditions. They may be seen in the acute state and sometimes represent an ictal pattern. The significance of PLEDs to predict prognosis may in part be due to limited amount of EEG in these patients to observe patterns of evolution and persistence of PLEDS. We reviewed patients with PLEDs during continuous EEG to ascertain relationship of morbidity to etiology and patterns of PLEDs.

Methods: Retrospective review of patients undergoing continuous EEG in our hospital from March, 2008 to September, 2009 who had PLEDs on EEG. Patient outcomes and subsequent EEGs were reviewed and analyzed which were recorded during and after a critical illness.

Results: Of 166 patients who had cEEG, 11(7%) patients had PLEDs pattern on EEG. Of the patients with PLEDs,7 patients died (64%) and of those that died the etiology consisted anoxic brain injury(42%), sepsis (42%), and bacterial meningitis (14%). Survivors of illness showing PLEDs (4 patients) had focal stroke in 3 and alcohol as etiology in one. Seizure patterns were seen slightly more frequently in the survivor group with no other difference in PLED patterns which persisted in many even after acute illness resolved or deficits persisted.

Conclusions: PLED patterns in themsleves are associated with acute illness but not may be able to prognosticate based on EEG features only. The occurrence of a more diffuse brain involvement by the underlying etiology copmpared to a focal vascular insult rather than the acute nature may be of more prognostic significance when occurring with PLEDs.

3.156

OPTICAL IMAGING OF PRIMATE NEOCORTEX USING OXYGEN SENSING NANOPARTICLES

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Rationale: Polymeric nanoparticles have recently been developed for quantitative, ratiometric imaging of oxygenation changes. This probe has previously been used for measuring oxygenation changes in tumor tissue. Our interest in adapting this technique for imaging the neocortex is twofold. First, imaging of oxygen sensing nanoparticles might be useful for mapping normal and epileptic neuronal activity. Second, this technique may prove to be a useful means for studying activity-evoked changes in tissue oxygenation and metabolism in neocortex.

Methods: The nanoparticles were prepared as previously described (Zhang et al., Nature Materials. 8:747-751, 2009). An imaging chamber was implanted that included hand motor and sensory cortex in the field of view. A 1.0 mg/ml solution of the nanoparticles in sterile water was prepared and applied to the exposed cortex in the imaging chamber. After 30 minutes, the nanoparticle solution was washed from the cortex and replaced with a layer of physiological saline solution.

The nanoparticle probe has an oxygen-insensitive fluorescence emission wavelength centered at 460nm, and an oxygen-sensitive phosphorescence emission wavelength at 540nm. Images were acquired for quantitative ratiometric measurements at both wavelengths during electrical stimulation of the cortex. Images of the intrinsic optical signal were also acquired at 535nm (blood volume) and 660nm (blood oxygenation) for comparison to images of the the cortex labeled with the oxygen sensing nanoparticles. Images were acquired while the cortex was electrically stimulated either below or above its afterdischarge threshold so that oxygenation changes could be studied in response to both normal and epileptiform activity.

Results: Ratiometric maps of the luminescent nanoparticle signals showed significant increases in the oxygenation of neocortical tissue during neuronal activity that was elicited by both subthreshold electrical stimulation and afterdischarge activity. The spatial and temporal patterns of oxygenation increases were similar to the intrinsic optical signal maps acquired at 535nm, but distinct from the intrinsic optical changes acquired at 660nm.

Conclusions: The oxygen nanosensors likely measure changes that occur near the cortical surface. These changes closely resembled the optical absorption changes measured at 535nm, suggesting that oxygenation increases in the upper cortical layers are the consequence of activity-evoked increases in blood perfusion. These results represent the first steps towards developing a new in vivo technique for mapping changes in tissue oxygenation in response neuronal activity. Since the oxygen sensing nanoparticles are nontoxic and biodegradable, they may potentially be useful for mapping functional and epileptic cortex during neurosurgical procedures.

3.157

NONINVASIVE IMAGING OF EPILEPSY USING FAST DIFFUSE OPTICAL TOMOGRAPHY

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Rationale: Along with hemoglobin changes, cerebral blood flow (CBF) and oxygen consumption (OC) changes resulting from functional activations are all important components of the hemodynamic response in epileptic seizure disorders. Malformations of cortical development (MCD) have been considered significantly as a major cause of seizures, which would demonstrate imaging contrast in cellular morphology imaging. Diffuse optical tomography (DOT) is able to retrieve 3D tissue functional and molecular properties noninvasively [Q. Wang et. al., 2008, Med. Phys. 35:216-224], which distinguishes it from intrinsic optical signal imaging where incision is required for imaging [S. Bahar et. al., 2006, NeuroReport 17:499-503]. Besides, DOT is able to reach a temporal resolution >1Hz, which gives this technology advantage over fMRI [Y. Aghakhani et. al., 2004, Brain 127:1127-1144] where important temporal information could be lost despite the fast varying brain activities.

Methods: A multispectral continuous-wave (CW) DOT system was applied in this study. Generally, filtered light (700nm and 750nm) from a white light source was delivered to multiple source points consequently on surface of the scalp area above the hippocampus. The screening site was imaged onto a CCD camera (CoolSNAP EZ, Photometrics) yielding a raw image of a 6x10mm area. Data acquisition time was about 750nm per frame (25 source points, single wavelength). A total of four rats were used in this study. For EEG control and source localization, 8 electrodes were implanted surrounding the imaging area for each rat. Anesthetized rats were mounted on a headset with ear bars and all hair on the scalp was shaved. Seizures were induced by intraperitoneal injection of pentyleneterazol (PTZ). DOT measurements made before the PTZ injection were used as calibration data and scans were conducted continuously for up to an hour after the PTZ injection, along with whole course EEG monitoring. A regularized nonlinear iterative reconstruction algorithm is applied for image recovery and analysis [C. Li et. al., 2007, App. Opt. 46:8229-8236].

Results: Figure 1 shows the reconstructed in vivo volume normalized CBF where the localized seizure focus has increased CBF (indicated by arrow). This is consistent with the general observation that epileptic seizures increase cerebral metabolism dramatically coupled with cerebral vessels dilations, while cerebral OC and CBF also increase secondary to the enhanced metabolic rate. For the reconstructed in vivo mean particle size images, significant quantitative changes over time have also been observed at the seizure focus.

Conclusions: In summary, we have developed effective system and models that are capable of estimating hemoglobin change, scattering particle size and volume fraction, as well as the CBF of biological tissues.

IMAGE: images/906797_A.jpg

Fig. 1 Reconstructed volume normalized CBF (ml/ml/s) images at different time points. Localized seizure onset is indicated by the arrow.

3.158

MORPHOLOGICAL AND QUANTITATIVE BRAIN ALTERATIONS INDUCED BY STATUS EPILEPTICUS: A LONGITUDINAL MR STUDY ON RAT BRAIN AT 7 TESLA

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Rationale: Brain insults like status epilepticus (SE) may lead to the development of chronic epilepsy and distinct neurodegeneration. MR relaxometry with T2 relaxation time mapping can be used to determine numeric T2 values of brain tissues, which is not only useful in scientific research, but also helpful as a sensitive diagnostic tool to examine microstructural alterations in the brain. Previous data have mainly been obtained at low field strengths. As MR systems with higher field strengths (> 3 T) become more common in research and clinical use, a reliable and practicable method for T2 mapping at such higher field strengths is needed.

Methods: To generate reference data, three naïve female adult Sprague-Dawley rats underwent four consecutive MR examinations on a 7 Tesla animal scanner (Bruker Pharmascan 70/16). The protocol included a T1-MDEFT sequence for imaging anatomic structures and two MSME-T2-map sequences containing different echoes, i.e. three versus 16 echoes, to find out the influence of echo numbers on T2 determination. T2 maps were obtained on a voxel-by-voxel basis using nonlinear least-squares fit. Quantitative T2 values of the grey and white matter were measured in exemplary regions of interest. Following baseline scans, rats were scanned immediately after a pilocarpine-induced SE which

lasted 90 minutes. During the next two days two animals died. The remaining rat was examined 48 hours, seven days and one, three, six and eight months later. Finally, we compared SE-induced alterations detected by MR with histological alterations in immunostained brain sections.

Results: In naïve rats, T2 values of about 49 ms for cortex and 40 ms for white matter were determined. No significant differences were found between the T2 values obtained from data of 16 echoes and those of three echoes ($p < 0.01$), although the signal-to-noise ratio was better by using the former. There was also no difference between values deduced from the repeated four MR examinations. Following SE, we observed dynamic brain alterations. Maximum cellular edema and swelling occurred 48 hours after SE, with visible lesions in temporal cortex, hippocampus, substantia nigra and thalamus. Interestingly, the hippocampal lesions showed a clear lamellar necrosis, indicating different vulnerability of the cellular structures. One week later, lesions were reduced, but global brain atrophy occurred and was still in progress until six months after SE. The measured T2 values confirmed these observations. First spontaneous seizures were detected about six weeks after SE.

Conclusions: This preliminary study shows that the T2 relaxation time measurements complement the morphological findings in the brain after SE. T1- and T2-weighted images sufficiently characterize changes in brain morphology after SE without inacceptable timeslots needed for longitudinal studies in larger animal groups.

3.159

MICROPET STUDY OF VERY EARLY REGIONAL GLUCOSE UPTAKE CHANGES IN LITHIUM-PILOCARPINE MODEL OF EPILEPTOGENESIS

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Rationale: Lithium-pilocarpine status epilepticus (SE) in rats heralds spontaneous recurrent seizures after a latent period. It therefore reproduces the temporal course of mesial temporal lobe epilepsy in humans. Focal ictal hypermetabolism and postictal hypometabolism are common findings in epileptic patients evaluated by positron emission tomography (PET). The aim of our study is to determine the very early modifications of regional utilization of glucose after SE using 2-[18F]-fluoro-2-deoxy-D-glucose small animal PET (microPET).

Methods: Young adult rats were subjected to lithium-pilocarpine induced SE (n=8). Controls were injected lithium and saline (n=7). Brain microPET (4 and 48 h after SE) and MRI (24 h after SE) were performed under isoflurane anesthesia. Regional glucose uptake was determined in 18 regions of interest formerly assigned on MRI. Results were normalized to brain global glucose uptake.

Results: All rats treated with lithium and pilocarpine became epileptic. Twenty four hours after SE, these animals exhibited dramatic T2 hypersignal in hippocampus, parahippocampal cortices, amygdala and thalamic nuclei. Four hours after SE, lithium-pilocarpine treated rats exhibited a significant increase in glucose uptake in CA3 (+17%) and parahippocampal structures: amygdala complex (+10%), piriform cortex (+ 23%) and entorhinal cortex (+14%). This hypermetabolism did not last since by 48 h brain global hypometabolism was recorded, more strikingly in para-hippocampal cortices (-23%).

Conclusions: Our study reproduced early MRI and microPET findings after lithium-pilocarpine induced SE. We also showed a transient increase in CA3 and para-hippocampal structures at the early acute phase of the SE. These regions are known to exhibit the marked neuronal loss in this model and to be key structures involved in epileptogenesis.

3.160

RATE DEPENDENT REGIONAL BRAIN ACTIVATIONS DURING INTERMITTENT LIGHT STIMULATION IN PHOTOSENSITIVE AND CONTROL NON-HUMAN PRIMATES

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Rationale: Although intermittent light stimulation (ILS) has been used for decades to activate photoparoxysmal responses in people with epilepsy, there is little data on frequency-dependent regional cerebral blood flow (rCBF) changes during ILS. As the baboon is the most extensively studied animal model of photosensitivity, we investigated the rate dependence of ILS-induced brain activations in both photosensitive (PS) and control (CTL) animals.

Methods: Eight baboons (5 PS; 3 CTL) underwent ILS at frequencies of 5 Hz, 10 Hz, 15 Hz and 25 Hz during concurrent H215O PET scans. The baboons were sedated using intravenous ketamine (5-6 mg/kg/hr) and paralyzed with vecuronium (0.1-0.3 mg/kg). The order of stimulations was randomized and two resting scans were performed before and after ILS. The images were analyzed using a combination of voxelwise statistical parametric images (SPIs) and correlation analyses. Group z-score images (SPI{z}) were obtained by comparing group-averaged resting scans and at each stimulation frequency. Activation and deactivation clusters were localized using each animal's MRI. Mean value normalized PET counts were obtained from volumes of interest (VOI) of >125 mm3 from the occipital, motor, posterior cingulate and orbitofrontal cortices and used for statistical parametric analyses. The mean counts were compared by two-tailed t-tests for differences in means.

Results: Activations were localized in the primary visual cortex, orbitofrontal and posterior cingulate cortices in PS animals. Mean PET count values for each of these areas demonstrated significant differences between each ILS frequency and baseline conditions between the two groups. Further analysis revealed an increase in PET counts with increasing ILS rates, with the primary visual regions peaking between 10-15 Hz in the CTL group, while PS baboons demonstrated maximal brain activations at 25 Hz. Connected regions (posterior cingulate and motor cortex) also demonstrated significant differences between the PS and CTL groups; rCBF increases with ILS frequency, dropping off at higher frequencies for the CTL group, whereas the PS group exhibited decreased rCBF with increasing ILS frequencies in these regions. The orbitofrontal regions demonstrated significant differences between the PS and CTL groups at 25 Hz.

Conclusions: In CTL baboons, peak activations of the visual cortex occurred at an ILS frequency of 15 Hz (compared to 10 Hz in humans). Occipital CBF peaked at 25 Hz in the PS baboons, which is the

frequency most likely to activate a photoparoxysmal response. Nonetheless, the regional CBF decreased in orbitofrontal and motor cortices at the same frequency, implying cortical inhibition related to interictal or ictal epileptic discharges. These findings support the use of a baboon model to investigate the mechanisms underlying ILS-induced physiological and photoparoxysmal responses in humans.

IMAGE: images/907837_A.jpg

Figure 1. Subtraction image of (ILS15Hz-Rest) conditions.

IMAGE: images/907837_B.jpg

Figure 2. Mean PET counts of sites associated with ILS-induced brain activations. Comparisons are between photosensitive and control groups. *(p d" 0.05) **(p d" 0.01).

3.161

EFFECT OF P-GLYCOPROTEIN FUNCTION ON CEREBRAL UPTAKE OF THE $GABA_A$-RECEPTOR LIGAND [^{11}C]FLUMAZENIL IN RATS AND MICE

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Rationale: [^{11}C]flumazenil, a $GABA_A$-receptor antagonist, is an important PET tracer for assessing GABAergic function in epilepsy by determining receptor density and affinity. Recently, several PET radioligands were found to be P-glycoprotein (P-gp) substrates (1-3). If this is also relevant for [^{11}C]flumazenil, increased P-gp function due to epilepsy could lead to changes in ligand uptake and thereby to erroneous interpretation with respect to GABAergic function. To this end [^{11}C]flumazenil studies were performed in naive and kainic acid treated rats (epilepsy model) as well as in wild type (WT) and P-gp knockout (KO) mice.

Methods: Rats received i.p. kainate injections to induce status epilepticus, 7 days before PET scanning. Naive animals received vehicle injections. WT and P-gp KO mice were not pretreated. Each animal underwent two consecutive [^{11}C]flumazenil scans, each of 30 minutes duration. Prior to the second scan, 15 mg.kg^{-1} tariquidar, a dose that completely blocks P-gp function, was administered i.v.. Brain concentrations of [^{11}C]flumazenil pre and post P-gp inhibition were compared.

Results: In rats, average whole brain [^{11}C]flumazenil concentrations increased 52% (range 31-90%) after tariquidar treatment. Kainate treated rats tended to have a somewhat larger increase in [^{11}C]flumazenil concentrations. This is in line with the hypothesis that these animals have an upregulated P-gp expression. P-gp KO mice had a 33% higher uptake of [^{11}C]flumazenil than WT mice. After P-gp blockage, [^{11}C]flumazenil concentrations increased with 51% in WT mice, while changes in P-gp KO mice were negligible.

These results indicate that [^{11}C]flumazenil is indeed a P-gp substrate. It should be noted, however, that more avid P-gp substrates, such as [^{11}C]verapamil, show a much larger (i.e. 10-fold) increase in brain concentrations after the same dose of tariquidar (4). Nonetheless, changes in P-gp function could potentially confound interpretation of [^{11}C]flumazenil scans.

Conclusions: [^{11}C]flumazenil is a moderate P-gp substrate. In a disease state such as epilepsy apparent altered binding of [^{11}C]flumazenil may be the result of changes in both $GABA_A$-receptor density and P-gp function.

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3.162

DIFFUSION TENSOR MRI IN ABSENCE EPILEPSY

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Rationale: Absence epilepsy involves abnormal interaction of corticothalamocortical networks. Diffusion tensor imaging (DTI) measures the diffusion properties of water in tissue and provides a noninvasive method for assessing white matter microstructure which allows detection of differences between healthy and non-healthy brains. The aim of this study is to assess potential morphological changes in childhood absence epilepsy (CAE) in human patients as well as in a well-established CAE animal model.

Methods: We performed DTI on children with CAE (n = 9) and age and sex matched normal children (n = 10). We used Wistar albino Glaxo rats of Rijswijk (WAG/Rij), a genetic model of CAE, without treatment (n = 10), and WAG/Rij rats after 4 months of chronic treatment (n = 9) started at age 30 day with the antiabsence medicine ethosuximide. Children were imaged on a 3T and rats on a 9.4T system. Data was processed using Bioimagesuite (www.bioimagesuite.org, Yale University, MRRC). Eigenvalues were calculated from the diffusion tensor matrix, and DTI metrics, including fractional anisotropy (FA) were determined. Registration of the imaging data (to a template brain from control group in each study) involved rigid-body and non-linear registration of T2-weighted structural images via a tensor b-spline algorithm; the composite transformation was then applied to all FA maps and other DTI metrics. FA maps were thresholded and a two sample t-test was performed to assess differences in FA between control and disease groups.

Results: Children with CAE show significantly decreased FA in the posterior white matter, forceps major region. The occipital and medial parietal cortices were found to be involved in separate fMRI studies of these children. Anterior corpus callosum of treated WAG/Rij rats showed increased FA compared to untreated WAG/Rij rats, suggesting there is some recovery in neuronal pathway morphology after

antiepileptogenic ethosuximide treatment. In another previous study, we found that the tissue integrity of the anterior corpus callosum was compromised in epileptic rats. Decrease in FA may involve reduced axonal density connecting and/or affected myelin integrity in this network connection intensely involved brain regions during absence seizures in children as well as in animal model.

Conclusions: Our studies show that DTI can detect subtle white matter changes due to recurrent spontaneous seizures in CAE children as well as improvement in white matter pathways in an animal treatment model due to antiepileptogenic ethosuximide treatment. These results are crucial for better understanding the CAE disease process and suggest that DTI may ultimately serve as a disease biomarker in a noninvasive manner in human therapeutic trials in absence epilepsy.

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3.163

FUNCTIONAL ACTIVITY OF GENERALIZED SPIKE-AND-WAVE DISCHARGES IN THE GBL RAT MODEL: AN EEG-FMRI STUDY

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Rationale: The generalized spike-and-wave discharges (GSWDs) are the result of irregular coupling between thalamic oscillations and cortical rhythms. However, the varying contribution of each cortical region to its clinical manifestations have not been well studied. This study is aimed to characterize the hemodynamic changes during GSWDs over time in order to better understand the dynamic processes that lead to the development of various clinical manifestations of absence seizures.

Methods: A pharmacological animal model was used. Animals were anesthetized using 1% isoflurane. Following 10 min simultaneous baseline scalp-EEG and 9.4 T fMRI recordings, GSWDs were generated in 8 Long-Evans rats using an intraperitoneal injection of ã-butyrolactone (GBL; 200 mg/kg). fMRI recordings were made for 60 min post-injection. EEG recordings were used to demonstrate the temporal occurrence of spiking and seizure activity, while general linear modeling, independent component analysis and dynamic causal modeling were implemented to characterize the hemodynamic changes and functional network abnormalities recorded using BOLD-fMRI.

Results: GBL produced bilaterally synchronous GSWDs within 2-5 min of its administration. We observed hemodynamic changes following GSWD onset in which there were unique patterns of activity specific to each brain area. The cerebral cortex showed a gradual and sustained increase in blood oxygenation in response to GBL injection preceding GSWD onset. A lesser effect was observed in the thalamic nuclei. Cortical hemodynamic "spiking" was also observed in some rats during SWDs.

Conclusions: Using simultaneous EEG-fMRI, we demonstrated robust hemodynamic signal changes in brain areas that have been electrophysiologically implicated in the generation of GSWDs. Hemodynamic "spiking" superimposed on the rise in the blood flow to the crebreal cortex was a novel finding that requires further studies.

IMAGE: images/903082_A.jpg

Brain areas of the rat showing increased BOLD signal changes following GBL injection. Statistical maps are overlaid on anatomical coronal slices. Slices are displayed from anterior to posterior (1-8).

IMAGE: images/903082_B.jpg

Independent component analysis (ICA) of fMRI data (single rat) following GSWD induction using a GBL model. (A) Spatial map of a component showing bilateral synchrony of the entire neocortex. The z-scores approximate the temporal correlation between each voxel and the associated temporal component where the magnitude of the z-score specifies the strength of the linear relationship. Z-scores maps are overlaid on raw functional images. (B) A segment of the corresponding time course of the spatial component showing slow "spiking" of the hemodynamic signal proceeding the electrical recordings of GSWDs.

3.164

SUBDERMAL EEG ELECTRODE PLACEMENT IN THE DOG USING NEURONAVIGATION

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Rationale: Electroencephalography (EEG) has been used in veterinary medicine for many years to detect pathological interictal and ictal activity. Although a ten-twenty system for electrode placement has never been developed in dogs due to variations in head sizes and morphology, several methods have been proposed to establish coherence between anatomical landmarks and electrode positioning. The purpose of this study was to evaluate an innovative and non-invasive method of positioning subdermal EEG electrodes in close proximity to the desired cortical areas in the dog (i.e frontal and temporal lobes).

Methods: A research dog was anesthetized to undergo brain MRI. Prior to MRI scanning, a dental bite block with laterally located fiducial markers was placed and secured in the dog's mouth. A 3D T1 weighted volume was acquired with the dog placed in sphinx position. Post-MRI, 3D image reconstructions of the brain, skull and skin were performed using Brainsight software. The dog was registered to his MRI scan by identifying homologous fiducial marker points using an optical position sensor and a neuronavigation pointer that displayed real-time images on a computer screen. Subdermal wiring EEG electrodes (SWE) were positioned in approximate locations under the scalp using an electrode montage routinely performed on a clinical basis without the use of the neuronavigation (Method 1). Localization of each electrode was then established to identify its position on the head and the underlying anatomical brain region using neuronavigation. The same electrode montage was then performed a second time using the navigation system to intentionally locate the SWE in direct proximity to desired cortical regions represented by electrode convention (ie. F3 = left frontal lobe) (Method 2). This second methodology was used as the gold standard for determination of accuracy in electrode positioning. The two techniques of electrode placement were then compared based on the overall mean electrode placement error represented in x, y and z between Methods 1 and 2 (Fig.1).

Results: The technique used in Method 1 demonstrated a variation in electrode positioning when compared to the gold standard Method 2. A total of 8 electrode sites were used for the analysis. The mean electrode

placement error for all SWE was 14.85 +/- 7.69 mm when comparing both methods. Frontal (F3 and F4) and parietal (P3 and P4) electrodes were most closely associated with the corresponding cortical lobes whereas occipital (O1 and O2) and temporal (T3 and T4) electrodes were the most divergent. In Method 1, three out of eight electrodes were placed over the wrong cortical anatomical region.

Conclusions: The use of a brain MRI compatible navigation system is an important technique to position EEG electrodes over their corresponding cortical anatomical lobe and strongly suggests that recorded EEG activity originates from the desired cortical area. This application may become useful for clinical and research purposes and may be extended to other species for comparative studies.

3.165

SEIZURE FREQUENCY IS RELATED TO BRAIN PERFUSION STATUS IN CHILDREN WITH STURGE-WEBER SYNDROME

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Rationale: Sturge-Weber syndrome (SWS) is a clinical model of early, chronic brain ischemia of venous origin, often associated with epilepsy. In this study, we used high-resolution perfusion weighted MRI (HR-PWI) to test if there is a quantitative relationship between cerebral perfusion deficits and clinical seizure variables in children with SWS.

Methods: Fifteen children with unilateral SWS (9 girls; age: 10 months - 10 years) prospectively underwent MR scanning including HR-PWI with a small voxel size of $1\times1\times4$ mm^3. Perfusion parameter maps of relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF) and mean transit time (MTT) were generated. rCBF, rCBV and MTT values in the subcortical white matter ipsilateral to the angioma, in regions affected by abnormal veins (pial angioma and deep veins), and in contralateral homotopic regions (avoiding the cortical surface, large vessels and ventricles) were measured. Asymmetry indices (AIs) for all three perfusion parameters were also calculated. All perfusion parameters ipsilateral to the angioma as well as perfusion AIs were correlated with seizure variables (age at epilepsy onset, duration of epilepsy, seizure frequency scores) using uni- and multivariate analyses.

Results: Mean age at seizure onset was 1.4 years, mean duration of epilepsy was 3.0 years (range: 0-9.7 years), and seizure frequency varied from less than once a year to daily seizures (frequency scores ranging from 1-5, with a median of monthly seizures). CBF asymmetries varied between +39% and -82%, while CBV asymmetries varied between +69% and -67%; increased rCBF values (all >20% increases in the affected hemisphere; mean AI: 31%±5%) were seen in 5 children, while 9 children showed decreased perfusion (mean AI: -36%±24%) on the side of the angioma (one child had symmetric perfusion). Longer duration of epilepsy was related to lower rCBF and rCBV (but not MTT) values in the affected hemisphere (for rCBF AIs: r=-0.57, p=0.025; for rCBV AIs: r=-0.52, p=0.048; for ipsilateral rCBV values: r=-0.65, p=0.009). Both rCBF and rCBV asymmetries also showed an inverse correlation with seizure frequency scores in univariate analyses (pd"0.01), and these correlations remained significant after epilepsy duration was controlled for (rCBF AI: r=-0.74, p=0.002; rCBV AI: r=-0.66, p=0.01). Age at epilepsy onset did not correlate with any perfusion variables.

Conclusions: Both increased and decreased perfusion can occur in the affected hemisphere in children with unilateral SWS. Increased perfusion can be present during the early course of the disease, while long duration of epilepsy is often associated with severe hypoperfusion. The results also indicate a strong relationship between seizure frequency and decreased brain perfusion in SWS, regardless of epilepsy duration. Chronic hypoperfusion and tissue hypoxia may play a role in seizure generation in SWS; frequent seizures may further aggravate brain ischemia and contribute to disease progression.

3.166

GLUTAMATERGIC DYSFUNCTION UNDERLYING HYPOMETABOLISM IN TEMPORAL LOBE EPILEPSY (TLE): A POSITRON EMISSION TOMOGRAPHY (PET) MULTIPARAMETRIC STUDY

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Rationale: Mesial temporal structures in TLE are classically characterized by low metabolism as indicated by [18F]FDG-PET. Although the mechanism underlying hypometabolism is not completely understood, changes in hippocampal glutamatergic neurotransmission might be related to the low energy budget found in the epileptogenic tissue. Post synaptic metabotropic glutamate receptor type 5 (mGLUR5) availability is reduced in the epileptogenic hippocampus (as measured by [11C]ABP688-PET). Here, we aim to test the hypothesis whether glucose metabolism determined by [18F]FDG-PET is linked to mGLUR5 availability measured by [11C]ABP688-PET.

Methods: We evaluated clinical [18F]FDG scans in 10 TLE patients who underwent a [11C]ABP688 scan (7 right, 3 left, lateralized according to their ictal EEG). [18F]FDG scans consisted in a 15min standard static acquisition followed [18F]FDG IV injection (4.5±0.58mCi). [11C]ABP688 scans consisted of a 1hour dynamic acquisition followed [11C]ABP688 injection (9.6±0.53mCi). Images were reconstructed using filter-back projection, and volumes were coregistered to each patient's MRI. ABP688-BP maps were generated using a simplified reference tissue method with the cerebellum as a reference region. FDG-uptake maps were normalized by the uptake at the pons. MRIs and maps were resampled to the standard space. Volumes of interest comprising the hippocampi (total structure, head and body) were manually drawn in each patient's MRI and used for extraction of mean FDG-uptake/ABP688-BP. We used paired samples 2-tailed t-test to determine differences between epileptogenic and contralateral structures, and 2-tailed Pearson correlation for FDG-uptake and ABP688-BP comparisons. Significance level was set at p=0.01.

Results: The epileptogenic hippocampi showed ABP688-BP of 79.23±5.7 (total), 76.17±7.7 (head) and 79.25±7.2 (body), whereas FDG-uptake was 0.6±0.03 (total), 0.58±0.03 (head) and 0.61±0.03 (body). At the contralateral side, hippocampal ABP688-BP was 105.62±6.54 (total), 113.35±6.5 (head) and 104.26±8.01 (body), whereas FDG-uptake was 0.64±0.02 (total), 0.63±0.03 (head) and 0.65±0.02 (body).

Epileptogenic hippocampi showed lower ABP688-BP as compared to contralateral side (df=9, t=-3.24, p=0.01), with higher difference identified in the head (df=9, t=-4.49, p=0.002). ABP688-BP was also

lower at the body, but not reaching significance. No differences in hippocampal FDG-uptake were observed.

Hippocampal FDG-uptake was correlated with ABP688-BP in the epileptogenic side (total R=0.895/p=0.0005; head R=0.789/p=0.007; body R=0.815/p=0.004) but not in the contralateral structure.

Conclusions: Our data strongly suggests a link between mGLUR5 availability and tissue metabolic processes, in the epileptogenic hippocampus only. Moreover, ABP688-BP seems to be more sensitive than FDG-uptake to identify the epileptogenic hippocampus in TLE. Our findings support a role of mGLUR5 in the mechanisms of epileptogenesis and links glutamatergic dysfunction to hypometabolism in the hyperexcitable hippocampus.

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INTERHEMISPHERIC CONNECTIVITY IN TEMPORAL LOBE EPILEPSY

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Rationale: Temporal lobe epilepsy (TLE) has increasingly proven to be a disease of brain networks, with mounting evidence hinting at the importance of connections between the affected medial temporal lobe and contralateral and/or extratemporal brain regions. Such connections may have either functional/compensatory or pathologic significance. Resting state BOLD fMRI has reliably demonstrated specific, reproducible brain networks in healthy controls. Here we used this technique to investigate whether the medial temporal regions in TLE patients show abnormal connectivity both intrinsically (within the temporal regions) as well as extrinsically with contralateral temporal brain regions.

Methods: Twelve patients with TLE (6 with left TLE, 6 with right TLE) were consecutively enrolled. Each patient had confirmed medial temporal epilepsy with hippocampal atrophy and EEG localization of seizures. Subjects underwent a resting-state BOLD fMRI session including 2-5 BOLD acquisition runs, each lasting approximately 6 minutes, acquired with a 3.0 T MRI scanner. During each BOLD run subjects were instructed to rest with their eyes closed. High-resolution structural T1 and T2-weighted images were also acquired for each subject for registration and atlas transformation. A group of healthy control subjects (n = 31) acquired under similar conditions was used for comparison. Eight regions of interest (ROIs) were defined a priori based on anatomical landmarks, including the entorhinal, hippocampal head, hippocampal body, and parahippocampal region in each hemisphere. Each ROI was used as a seed in a functional connectivity analysis using typical methods (e.g. Fox et al., J. Neurophysiol., 2009, 101:3270-83). Voxelwise connectivity maps for each seed were used to compute connectivity strength between regions. These measures were entered in a random effects model.

Results: Results showed significantly decreased connectivity ($p < .05$) in the anterior medial temporal ROIs (entorhinal and hippocampal head) of the affected hemisphere compared to the contralateral hemisphere. Interestingly, the affected hippocampal head showed stronger connectivity with the contralateral hippocampal head than with the ipsilateral medial temporal regions (entorhinal, hippocampal body, and parahippocampal regions). This suggests both reduced functional cross-talk between the diseased hippocampal head and neighboring medial temporal regions, and increased functional communication with the contralateral hippocampal head, possibly in compensatory fashion.

Conclusions: Preliminary results argue for a potential marker of focal medial temporal pathology in the form of locally reduced functional connectivity, which may aid in localization for diagnosis and presurgical planning, as well as for assessment of therapy effects. Furthermore the noted strong interhemispheric connectivity suggests the existence of partially preserved function in the affected hippocampal head. Tracking the amount of preserved connectivity in TLE-affected regions at the individual subject level may help predict which patients are at greatest risk of postsurgical functional decline.

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EEG/FMRI IN FOCAL EPILEPSY: WHAT DOES THE BOLD RESPONSE ADD TO EEG?

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Rationale: Simultaneous EEG and functional MRI (EEG/fMRI) is a non-invasive technique with which it is possible to detect hemodynamic changes related to interictal epileptic discharges (paroxysmal slow waves, sharp waves or spikes: IED) identified on scalp EEG. It has been suggested as a useful tool to characterize various forms of focal and generalized epilepsy and may help in the pre-surgical evaluation of patients with refractory focal epilepsy. To better investigate how much the EEG/fMRI is useful in clinical practice, we studied the information that the BOLD adds to the definition of the epileptogenic zone in patients with focal epilepsy.

Methods: Consecutive patients with focal epilepsy who underwent EEG/fMRI from April 2009 to April 2010 were retrospectively reviewed. All underwent a 120 min recording session (anatomic acquisition and BOLD fMRI data collected in runs of 6 min with the patient resting). EEG was recorded inside the 3T scanner. For each patient IEDs similar to those recorded outside the scanner were marked by a single electroencephalographer in the filtered EEG. IEDs with different shape or distribution were analyzed as separate event types. The epileptogenic zone was classified as localized, lateralized, bifocal, or uncertain on the basis of seizure semeiology, video-EEG telemetry, MRI, and in some patients SEEG. BOLD responses were reviewed by three experts. The BOLD responses were classified as “not contributory” if clearly suggestive of an artifactual pattern or if the BOLD map provided no new information compared to the scalp EEG, and “contributory” if at least one of the marked event types for each patient provided additional information to the EEG about the focus. We considered patients having SEEG, two EEG/fMRI sessions or a focal lesion on MRI as having independent validation (IV).

Results: Thirty-one patients were included. In 8 the EEG was not active during the acquisition. The remaining 23 had at least 1 type of IED. Thirteen of 23 had IV (7 SEEG, 3 focal lesion, 3 repetition of the test) and in all cases the BOLD results were confirmed. In 5/23 the BOLD response was “not contributory” (2 cases with generalized EEG and concordant generalized BOLD, without added information, and 3 with artefactual patterns). In 18/23 the BOLD response was “contributory”: 13/18 had focal EEG and focal BOLD response with IV, 4 had focal EEG and focal BOLD response concordant with the epileptogenic zone without IV, 1 had generalized EEG and focal BOLD response without IV. In all focal cases, the BOLD response allowed a more precise definition of the source of IEDs than could be obtained from scalp EEG.

Conclusions: In ¼ patients the examination was useless because no IED was recorded. Considering the remaining 23 patients, in only 5 cases BOLD responses did not provide additional information. In all patients with IV the BOLD responses were strongly corroborated. We therefore assume that in patients without IV, BOLD also provided valid results. With this assumption, more specific localization was gained from EEG/fMRI in 18/23 cases (78.3%), when compared to scalp EEG.

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SIMULTANEOUS EEG-FNIRS RECORDING OF DORSOLATERAL FRONTAL LOBE SEIZURES

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Rationale: Frontal lobe epilepsy represents approximately 30% of partial epilepsies seen in epilepsy centers and is the second most common type of epilepsy treated surgically. However, outcome after surgery has been less than satisfying. Possible explanations include the imprecise localizing value of the various seizure patterns originating from the frontal lobes and the presence of a functional network of pathways permitting rapid ictal spread within and outside the frontal lobe making precise localization of ictal onset difficult. Functional near-infrared spectroscopy (fNIRS) is a non-invasive imaging technique of potential value in the study of epileptics. Its temporal resolution (20Hz) offers the possibility to study the evolution of hemodynamic changes occurring during seizures and follow their spatial propagation over time. We report here on the hemodynamic behavior observed in a group of patients with dorsolateral frontal lobe epilepsy.

Methods: Patients were diagnosed with dorsolateral frontal lobe seizures based on multimodal analysis of clinical history, video-EEG monitoring, ictal SPECT, EEG-fMRI, MEG-EEG and intracranial recordings.

EEG-fNIRS recording using 19 EEG in-house electrodes (EEG video-monitoring; Compumedics, USA) combined with 60 to 140 fNIRS channels (ISS, USA) in order to cover frontal, temporal and parietal lobes bilaterally. Seizure onsets and end times were marked as the earliest and latest scalp electrographic evidence of seizure activity. Hemoglobin concentration variations were calculated and analyzed with the Homer Matlab package and viewing tools developed in-house.

Results: Several electrical and electroclinical seizures were successfully recorded using EEG-fNIRS from three patients (age 13 to 43, 2 males /1 female) with refractory dorsolateral frontal lobe epilepsy. All these events were easily distinguishable by fNIRS as independent increases and decreases in fNIRS signal. A great degree of variability was observed both inter subject, and intra subject for successive ictal events. In general however, a significant increase in oxyhemoglobin concentration ([HbO]) is seen at seizure onset over bilateral dorsolateral frontal regions, slightly predominant and earlier ipsilaterally. Concomitantly, mild increases in deoxyhemoglobin concentration ([HbR]) are noted. The initial increase in [HbO] is followed by a significant decrease after a few seconds. In distant temporal and parietal regions, a rapid and sustained decrease in [HbO] is seen. Although seizures were short in duration on scalp EEG, hemodynamic changes inferred by fNIRS were systematically longer. Electrical seizures had better localizing potential than electroclinical seizures because of lesser propagation of hemodynamic changes.

Conclusions: Preliminary hemodynamic observations of dorsolateral frontal lobe seizures using EEG-fNIRS suggest a) easily detected rapid changes of [HbO] and [HbR] at onset; b) generally (but not always) earliest in the region of seizure onset and; c) with rapid ipsi- and contralateral propagation, especially with electroclinical seizures as opposed to electrical seizures.

3.170

[18F]-FLUMAZENIL-PET FOR THE LOCALISATION OF MEDICALLY REFRACTORY FOCAL EPILEPSY USING WITHOUT NEED FOR ARTERIAL BLOOD SAMPLING: A PILOT STUDY

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Rationale: [11C]-flumazenil-PET (FMZ-PET) has proven to have high sensitivity for localisation of the epileptogenic zone (EZ) in patients with medically refractory focal epilepsy, with a more restricted region of abnormality that FDG-PET. However, practical aspects of [11C] and requirement for arterial blood sampling have limited its clinical application. We have developed a method utilising a new radioliogand, [18F]-FMZ, that does not require arterial blood sampling. In the current study we have assessed [18F]-FMZ-PET for localisation of the EZ in patients with medically refractory focal epilepsy.

Methods: Four subject groups were studied; healthy controls (n=20), patients with well-localised temporal lobe epilepsy (TLE) with hippocampal sclerosis on MRI (n=12), patients with well-localised TLE and normal MRI (n=14), and patients with other focal epilepsies (n=4). A 60min dynamic [18F]-FMZ-PET scan and an FDG-PET scan were acquired. Blinded visual assessment of static images was undertaken. Parametric images of binding potential (BP) were generated and region of interest analysis and statistical parametric mapping (SPM) used to localise the EZ.

Results: Visual assessment of static images has shown [18F]-FMZ-PET to have high specificity (94%), sensitivity (60.9%) and positive predictive value (87.5%) for the EZ, with a more restricted EZ compared to FDG-PET. Initial SPM results also depict a more restricted area of abnormality on FMZ BP images than FDG; regional analysis is ongoing.

Conclusions: Preliminary analyses show that [18F]-FMZ may have improved localisation of the EZ compared with FDG, indicating its potential as a new clinical tool for the evaluation of patients for epilepsy surgery.

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IMAGING ICTAL RHYTHMIC ACTIVITY USING HIGH-DENSITY EEG

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Rationale: Long-term EEG monitoring is a major component of the pre-surgical evaluation of medically intractable epilepsy. However, this procedure suffers from low spatial resolution, and alone is often inadequate for the precise delineation of the epileptogenic brain. We report a novel spatiotemporal source imaging approach for localizing and tracking seizure activity using long-term, 76-electrode scalp EEG monitoring (dense-array EEG) . Direct imaging of seizure sources and their dynamics may improve surgical management of intractable epilepsy, and make high density EEG imaging a pre-surgical evaluation tool in the epilepsy treatment.

Methods: Five adult patients underwent continuous video EEG monitoring using 76 channels. They all had high-resolution MRI prior to the surgery. Four patients underwent resective surgery and all became seizure free. Post-operative MRIs were collected for these four patients. Three patients underwent intracranial EEG monitoring, including the one without resective surgery. In the source imaging analysis, ictal EEG segment was decomposed using independent component analysis (ICA). The scalp map of each independent component (IC) was used to estimate the 3D brain source distribution by solving an EEG inverse problem. The time course of each IC was used to compute a spectrogram, and components showing time-frequency evolution of ictal rhythmic discharges were selected. As an inverse process of ICA, we re-combined the IC source distributions and IC time courses in 3D source space, which resulted in a spatiotemporal estimation of the brain ictal source activity.

Results: A total of 11 seizures were analyzed. The seizure onset zone (SOZ) was localized for each patient as the source distribution at the time of seizure onset. In each of the four patients who underwent resective surgery, significant overlap was observed between the estimated SOZ and the resected brain volume, and furthermore the maximal estimated source point was localized within the resected region. In the patient not undergoing resective surgery, the estimated SOZ was concordant with epileptogenic brain determined by intracranial EEG and SPECT. In the three patients with intracranial electrodes, the seizure onset and propagation pattern estimated by source imaging was concordant with the intracranial recording.

Conclusions: The results obtained in this study have potential implications for the practice of pre-surgical evaluation of epilepsy. The feasibility of obtaining ictal recordings from a 76-channel EEG montage was successfully demonstrated in a cohort of 5 patients. The clinical data was recorded over 6±4 days, and the 76-electrode montage successfully captured each seizure in this cohort of patients. With dense-array EEG the proposed seizure imaging technique makes possible direct imaging of the generators of seizures and their propagation. With the capability of recording and imaging ictal activity, the proposed high-density recording and electrographic seizure imaging technique provides a non-invasive imaging tool to assist pre-surgical planning in the treatment of medically intractable epilepsy.

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HIGH TEMPORAL RESOLUTION PHOTOACOUSTIC IMAGING FOR SEIZURE LOCALIZATION AND NETWORK MAPPING

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Rationale: Our previous study showed that photoacoustic tomography (PAT), an emerging imaging modality with unique ability of imaging biological tissues with high optical contrast and high ultrasound resolution, is able to image seizure-onset zone in an animal model of focal seizures. To provide three-dimensional (3D) real-time hemodynamic information such as blood oxygenation and blood volume, a PAT system based on a cylindrical ultrasound transducer array has been built. Tissue-like phantom has been used to validate the high speed imaging system and in vivo animal imaging has been performed using a bicuculline methiodide (BMI) animal model of epilepsy.

Methods: A cylindrical transducer array with 192 elements was employed for collecting the light induced acoustic signals. The laser beam from a pulsed Nd:YAG laser with 4ns pulse duration was expanded to 3cm diameter thus to apply a light power of 15mJ/cm2 at the surface of the phantom/rat head, which was lower than the maximum permissible exposure for skin (20 mJ/cm2). The collected acoustic signal was amplified by 192-channel preamplifiers and then digitized by a 64-channel parallel data acquisition system with 50MHz sampling rate and additional 60dB gain. A full set of 3D photoacoustic data can be obtained at every three fires of the laser. Tissue-like phantoms have been used to validate and optimize this fast imaging system. Animal PAT data were obtained from several young male rats weighing 50~60g using urethane anesthesia (1mg/g). Acute seizure foci were induced by the injection of BMI over the frontal neocortex and confirmed with EEG. Continues photoacoustic data was been collecting for 30 minutes after the BMI injection.

Results: The tissue-like phantom results obtained showed that the fast PAT system could obtain high spatial resolution absorption images at 10Hz.

In the animal experiments, focal seizures were induced by microinjections of BMI into one side of parietal cortex and confirmed with EEG recordings which showed high amplitude spike and wave discharges. PAT images were recovered from data obtained at 10Hz within 30 minutes after the BMI injection. Large increase of absorption was observed in a region around the location of BMI injection in two to five minutes which reflected the increasing of blood flow in the same area. These seizures were accurately localized by PAT. The dynamic changes in PAT imaging were comparable to EEG changes during seizures.

Conclusions: Our results showed that by using the fast PAT system seizure foci in rats could be imaged at a speed of 10Hz and a spatial resolution of 400ìm. The imaging speed of the system can be improved to up to 200Hz by employing a faster laser source available commercially. The ability of functional imaging at a spatial resolution comparable to MRI and at a temporal resolution comparable to EEG makes high speed PAT a powerful tool in the studies of epilepsy.

3.173

METABOLIC AND MOLECULAR IMAGING CHARACTERISTICS OF EPILEPTOGENIC DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMORS (DNETS)

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Rationale: DNETs are low-grade, epileptogenic tumors with low glucose metabolism on PET. Our recent studies showed accumulation of á[^{11}C]methyl-L-tryptophan (AMT), a PET tracer for the immuno-modulatory kynurenine pathway, in epileptogenic malformations and some DNETs. In this study we used 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG) and dynamic AMT PET scanning to evaluate the relation between glucose metabolism, AMT transport and metabolism as well as clinical seizure variables in children with epileptogenic DNETs. Resected DNET specimens were also studied for the presence of L-type amino acid transporter 1 (LAT1) and indoleamine 2,3-dioxygenase (IDO; a key enzyme of the kynurenine pathway).

Methods: Twelve children (age: 2.5-17.5 years) who underwent resective surgery due to epilepsy associated with a DNET were included in the study. Tumors were outlined on MRIs and tumor volumes were calculated. The same tumor regions were superimposed on co-registered FDG and AMT PET images to obtain standardized uptake values (SUVs) and SUV ratios (tumor/contralateral cortex). Furthermore, kinetic parameters of AMT uptake characterizing the tracer transport (by the volume of distribution [VD]) and metabolic rate (by the unidirectional tracer uptake [K-complex]), as well as corresponding tumor/cortex ratios were also calculated in 10 patients and correlated with seizure variables. Resected tumor specimens were immuno-stained for IDO and LAT1.

Results: Tumor volumes varied from 0.8 to 51.4 cm^3 (median=4.2 cm^3). All tumors showed glucose hypometabolism on FDG PET scans (SUV ratio: 0.29-0.64). However, tumor AMT SUV values were above cortical values in 8/12 cases (0.87-1.44) (Figure). Two patients showed increased AMT SUV in additional ipsilateral cortical areas. Kinetic analysis of AMT PET showed increased VD ratios in 8/10 children and high K-complex ratios in 3. Age at seizure onset showed a positive association with FDG SUV of the tumors (r=0.68; p=0.016, Spearman's correlation). Longer epilepsy duration was associated with higher AMT K-complex values in DNETs (p=0.036). Tumor volumes did not correlate with any clinical and PET variables. Nine children had seizure-free outcome, while 3 had recurrent seizures, including the two cases with preoperative cortical AMT increases in areas which were not resected. All tumor specimens showed moderate to intense IDO and LAT1 staining.

Conclusions: Despite low glucose metabolic rates and variable sizes, DNETs commonly show high AMT accumulation on PET, which is mostly driven by increased tryptophan transport but also due to tryptophan metabolism. Activation of kynurenine pathway may contribute to immune-resistance of these tumors but can also produce neurotoxic/epileptogenic metabolites. Association of higher tryptophan metabolic rates with longer epilepsy duration suggests a progressive activation of this pathway providing a potential therapeutic target for these lesions. In addition, AMT PET may detect potentially epileptogenic cortex outside DNETs in some cases; this may help optimize surgical resection to facilitate seizure-free outcome.

IMAGE: images/905937_A.jpg

3.174

SIMULTANEOUS EEG AND FMRI OF SLEEP SPINDLES AND K-COMPLEXES

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Rationale: Spindles and K-complexes are spontaneous EEG markers of non-rapid eye movement (REM) sleep that first appear in stage 2.They are believed to arise from thalamo-cortical networks involving thalamic reticular nucleus and they are likely related to sleep preservation.K-complexes may be elicited by environmental stimuli and spindles may inhibit perception of environmental stimuli.However,the regions generating the discharges and the functional connections of the generators to other regions are not fully known. Simultaneous EEG and fMRI provides depiction of brain regions with functional change during EEG events, and we used this technique to localize fMRI signal changes corresponding to spontaneous spindles and K-complexes.

Methods: We reviewed 98 EEGs from 29 participants recorded during fMRI according to an IRB-approved protocol to investigate the anatomy of EEG activity.Spindles and K-complexes were identified and fMRI data analysis was performed using fMRI Software Library (FSL, Oxford, UK) by convolving the transients' occurrence time with a double-gamma hemodynamic response function. Higher level group analysis was performed with a mixed effects approach. Images were thresholded at Z value of 2.3.

Results: A total of 106 spindles and 68 K-complexes were identified within the EEGs of 7 participants who had spontaneous, deep sleep. Among the participants, 5 had epilepsy and 2 were controls without neurologic disease. The spindles appeared during 16 EEGs and the K-complexes during 18 EEGs.Image analysis of the spindles identified increased signal in bilateral thalamus, superior pre- and post-central cortex, posterior cingulate, pre-cuneus, and right superior temporal. Analysis of the K-complexes identified increased signal in bilateral thalamus, superior temporal, pre- and post-central cortex, and medial regions of the occipital, parietal and posterior frontal lobes. No regions of decreased signal occurred.

Conclusions: The thalamic signal for both spindles and K-complexes is consistent with existing understanding of the role of each discharge in sleep preservation through gating sensory awareness. However, the thalamic finding for the K-complexes may still be related to the spindle associated with each K-complex because the fMRI temporal resolution does not allow differentiation of events occuring in the same TR. Each discharge also corresponds to signal subjacent to the EEG event, which most likely indicates a common neocortical generator. K-complexes include a broader extent of signal, encompassing primary sensory cortex for vision, touch, and hearing, and this may indicate an additional gating effect specific for the distinct sensory cortices. Asymmetric temporal signal corresponding to the spindles is unexpected and may be due to the contralateral temporal signal not reaching significance. Signal in this region had a Z value of 2.0. Additional investigation is needed to address this. Identification of the anatomic regions involved in spindle and K-complex generation may advance the understanding of thalamic networks and the electrophysiology of awareness during sleep.

IMAGE: images/876335_A.jpg

fMRI signal changes of 106 spindles from7 subjects. Z value 2.3

IMAGE: images/876335_B.jpg

fMRI signal changes for 68 K-complexes from 7 subjects. Z value 2.3

3.175

MEMORY DYSFUNCTION IN FRONTAL LOBE EPILEPSY. THE ROLE OF FRONTAL LOBES IN LONG TERM MEMORY PROCESS

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Rationale: A high degree of overlapping has been documented between the cognitive profiles of FLE and TLE patients. Cognitive and neuroimage studies have showed that TLE causes local damage to temporal lobe structures but also remote functional and structural abnormalities on frontal lobes suggesting speeded damage to cortical areas beyond the epileptic focus. To our knowledge, no studies assessing the extension functional damage has been carried out on FLE population.

Objectives:

To study the effect of frontal lobe epilepsy on the functional networks involved on memory encoding. In particular we will study the local effect of seizure focus on frontal lobe and the remote effect of epilepsy on temporal lobe networks activated during memory encoding.

To study the profile of memory impairment on FLE.

Methods: We studied 39 FLE patients (19 with left 15 with right epileptic foci and 5 non lateralized) and 20 healthy volunteers using a memory encoding fMRI paradigm on a 3T scanner followed by a recognition test out of the scanner. Activation maps for the blocks of different stimuli and for the events successfully remembered where created with SPM5 software and compared between groups. Analysis of performance and neuropsychological evaluation was carried out.

Results: Patients with FLE are impaired on memory tasks of long term recognition and verbal and non verbal learning. Memory impairment on FLE is not material specific.

Maps of activation showed no differences on the activation of medial temporal structures between controls and FLE patients.

FLE patients recruited wider areas of activation including mid frontal gyrus, perisylvian cortices and SMA during the presentation of to memorize items. These activations are mainly located on the contra lateral frontal lobe to the epileptic focus.

Conclusions: Activation of mid temporal structures during a memory tasks in FLE patients is comparable to controls. Our results does not show evidence of dysfunction of mesial temporal structures on FLE.

FLE patients recruit wider areas during the task suggesting a possible compensatory mechanism of the frontal lobe dysfunction.

3.176

ICTAL BOLD CHANGES AND BEHAVIORAL PERFORMANCE VARIABILITY IN CHILDHOOD ABSENCE EPILEPSY

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Rationale: Seizures in childhood absence epilepsy (CAE) are characterized electrographically by epochs of 3-4 Hz spike-and-wave discharges and semiologically by impaired consciousness. Although absence seizures have historically been categorized as generalized events, recent work has demonstrated a complex timecourse of focal changes in the brain, particularly within the attention network including the orbital/medial frontal cortex, medial/lateral parietal cortex and thalamus. In addition to subtle electrographic differences in absence epilepsy across seizures and between patients, considerable variability also exists in ictal blood oxygen level-dependent (BOLD) signal changes and behavioral performance. We propose that the selective disruption of attentional networks, as captured by BOLD signal changes, is related to the degree of behavioral impairment during absence seizures.

Methods: Using simultaneous electroencephalography and functional magnetic resonance imaging (EEG-fMRI), we examined ictal changes for 175 seizures in 13 pediatric patients with CAE. During each scan, patients performed a continuous performance task (CPT) or a simpler repetitive tapping task to measure impaired attention. BOLD signals changes were analyzed using statistical parametric mapping (SPM) and in-house software.

Results: As expected, patients' performance during SWD was impaired, and this impairment was more pronounced during CPT than RTT. fMRI changes seen during seizures were consistent with those demonstrated in previous studies. Specifically, we observed a complex sequence of changes in orbital frontal, parietal, and other cortical areas as well as the thalamus. The timecourse of ictal BOLD changes and behavioral performance were highly variable across patients and seizures and were not obviously correlated with the EEG measures. An analysis of the EEG recordings revealed a possible link between seizure duration and the degree of ictal impairment. Interestingly, however, omission errors were committed even during brief spike-wave seizures.

Conclusions: Focal fMRI changes in cortical and subcortical attention structures appear to be related to variability in task performance during seizures. This relationship can shed light on the mechanism by which absence seizures cause impaired consciousness and could guide development of targeted therapies.

3.177

INTERACTION OF THE NETWORKS SUSTAINING EPILEPTIC DISCHARGE AND MEMORY FUNCTION IN TEMPORAL LOBE EPILEPSY

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Rationale: Temporal lobe epilepsy with hippocampal sclerosis is a chronic disease with frequent neuropsychological deficits. It is widely acknowledged that physiological brain function in these patients is jeopardized both by acute epileptic activity and changes in neuronal circuitry. The latter changes have received much recent interest with the advent of diffusion tensor imaging (DTI). Several DTI-studies showed correlations between alterations of white matter connectivity and memory impairment, most notably in cases of left hippocampal sclerosis. However, the precise functional topography of the changes in memory circuitry remains yet to be established.

Our study intended to probe common patterns of functional memory activations in left and right hippocampal sclerosis and relate them to the underlying structural connectivity of the affected hippocampus.

Methods: We have gathered a large data base on a homogeneous group of patients with unilateral sclerosis, comprising 22 patients with left and 22 patients with right sided lesions and 22 matched control subjects. We recorded DTI sequences with 50 directions and functional MRI (fMRI) of memory function. In short, nameable object stimuli were encoded 24h prior to the recognition session, which was scanned at 3T. Over all subjects, bilateral dorsolateral prefrontal and temporal occipital cortex as well as Broca's area were implicated in delayed object recognition. These cortical hotspots serve as regions of interest in a current second analysis. Here individual hippocampi are segmented and used as seed regions for probabilistic tractography between the hippocampus and the said cortical regions of interest.

Results: Second level analysis between groups of patients revealed differential activation of distributed memory landmarks. Patients with right hippocampal sclerosis had enhanced BOLD signal in the left sided memory network, most notably in temporo occipital regions. Patients with left hippocampal sclerosis, on the contrary, showed enhanced activation in the inferior parietal region ipsilateral to the lesion. This area has been implicated in hippocampo parietal networks of episodic memory (Vincent et al., 2006). These data suggest differential remodeling of the cortical memory circuitry, which is more pronounced in left temporal lobe epilepsy. Preliminary analysis of structural connectivity points to a de-afferentation of the lesioned hippocampus from ipsilateral frontal and temporal occipital areas.

Conclusions: Patients with left or right hippocampal sclerosis show differential reorganization of memory circuitry which essentially concerns the left hemisphere of patients with left sided lesion, possibly due to de-afferentation of the affected hippocampus. These results improve our insight into the interaction of epileptic and cognitive networks and help to establish a blueprint of individual functional and structural memory topography in hippocampal sclerosis.

3.178

LANGUAGE LATERALIZATION IN PATIENTS WITH TUBEROUS SCLEROSIS COMPLEX (TSC) USING MEG AND FMRI

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Rationale: TSC is a multisystem genetic disorder. Brain abnormalities include cortical tubers, which can be epileptogenic. Nearly 90% of patients with TSC have epilepsy and 2/3 of them are refractory to pharmacotherapy. Epilepsy surgery can be considered and requires a presurgical workup that may involve assessment of language lateralization. Noninvasive techniques, such as functional MRI (fMRI) and magnetoencephalography (MEG) are now used to assess language lateralization in epileptic patients. This is the first study to investigate language lateralization in a group of TSC patients using MEG and fMRI.

Methods: Fifteen patients with TSC performed a lexico-semantic decision task during MEG and fMRI recordings. MEG data was acquired from a 306-channel whole-head MEG system. Standard BOLD fMRI and anatomical MRI scans were performed on a 1.5T scanner. MEG data was co-registered with structural MRI using fiducial points from a 3D digitizer. The lexico-semantic task consisted of a sequential visual presentation of 160 words. Patients were asked to respond manually by pressing the right button on a response pad if the presented word was concrete (ex: apple) and the left button if the word was abstract (ex: freedom). A digital band pass filter of 0.1-40Hz was applied off-line. Data were averaged across all 160 trials without distinction between concrete and abstract words. Minimum-norm estimates (MNE) were computed using MNE software (version 2.5, Hamalainen, 2006) allowing identification of cerebral generators of language evoked fields (EF) in each patient. Laterality indices (LI) were computed by comparing MNE amplitude between 250 and 550 ms in the inferior frontal, middle and superior temporal, inferior parietal and supramarginal gyri from both hemispheres. LI > +0.10 was interpreted as left, LI < -0.10 as right, and LI between -0.10 and +0.10 as bilateral language dominance. MEG results were compared to fMRI data acquired while the patients performed the same task. fMRI data were analyzed using FSFAST software.

Results: MNE showed language cerebral activations starting in the middle and superior temporal gyri traveling progressively to the inferior frontal gyrus in all patients. Inferoparietal and supramarginal activations were also measured in most patients, although these activations were weaker compared to frontotemporal responses. A perfect concordance between MEG and fMRI LI was obtained for all patients. As also found with fMRI, fourteen patients had left language lateralization on MEG results (LI between 0.11 and 0.44) and one patient showed a bilateral language dominance (LI = 0.05).

Conclusions: This is the first neuroimaging study to investigate language lateralization in a group of patients with TSC. A perfect concordance between MEG and fMRI results for language lateralization was obtained in all 15 patients using a lexico-semantic task. Compared to fMRI, MEG provides temporal information that helps better understand cerebral language activations. MEG may constitute an alternate means of safely investigating language lateralization in TSC patients.

3.179

HIPPOCAMPAL NETWORKS IN TEMPORAL LOBE EPILEPSY: A 'SEED-BASED' FMRI STUDY

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Rationale: Intracerebral recordings have suggested alterations of hippocampal networks in temporal lobe epilepsy (TLE). We evaluated the hippocampal networks in TLE non-invasively using resting state functional MRI (fMRI) connectivity analysis, a technique that

analyzes hemodynamic coherence of a 'seed area' and maps the underlying associated network.

Methods: Regions of interest were identified in both the left and right hippocampi to be used as seeds to develop coherence maps in resting state MRIs of 5 subjects with right TLE (R-TLE), 5 with left TLE (L-TLE), and 6 control subjects. Pair-wise tests were done between the 3 groups separately for each seed analysis. The coherence maps were compared by a whole-brain independent t-test, and corrected for multiple comparisons by cluster correction ($z > 2.3$, $p < 0.05$). Analyses used FSL (FMRIB's Software Library, Oxford University, UK).

Results: Compared to controls, patients with R-TLE and L-TLE demonstrated decreased left hippocampal connectivity to bilateral medial occipital areas and the precuneus, and increased right hippocampal connectivity to the periventricular white matter. Comparison between R-TLE and L-TLE did not show significant differences.

Conclusions: A novel fMRI technique of investigating functional networks in TLE demonstrated reduced connectivity of the left hippocampus to occipital networks and increased connectivity of the right hippocampus to periventricular white matter. These changes were similar in both L-TLE and R-TLE suggesting that these network-level changes are likely a function of the disease (TLE) and not based on lateralization.

IMAGE: images/906390_A.jpg

3.180

DIMINISHED RECRUITMENT OF HIPPOCAMPUS INTO DEFAULT MODE NETWORK IN TEMPORAL LOBE EPILEPSY

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Rationale: The default mode network (DMN) is a network of brain regions that are spontaneously active when an individual is at wakeful rest. The DMN has a central hub of the posterior cingulate cortex which recruits the ventral medial prefrontal cortex, inferior lateral parietal cortex, and the bilateral hippocampi. Frings and colleagues (2009) showed reduced connectivity between posterior cingulate and left hippocampus in patients with left mesial temporal sclerosis (MTS), although this finding did not extend to right-sided disease. Given intersubject variability in the strength of DMN functional connectivity, we propose an interhemispheric difference in hippocampal DMN recruitment in TLE. Specifically, we expect the affected hippocampus to be less strongly incorporated into DMN than the unaffected hippocampus; and this trend to exist in TLE patients but not healthy control participants.

Methods: 15 TLE patients (age= 38+-14 years; 7 male; 5 [33%] with unilateral hippocampal sclerosis) and 18 healthy control subjects (age= 36+-12 years; 5 male) underwent a resting state fMRI scan. During the resting state scan, participants were instructed to clear their minds of any specific thoughts and passively view a fixation cross. Regions of interest (ROIs) were defined as 6mm radius spheres for the midline posterior cingulate (PCC), midline medial prefrontal cortex (MPFC), ipsi- and contralateral hippocampus (iHPC, cHPC), and ipsi- and contralateral inferior parietal (iPAR, cPAR). For controls, right hemisphere was arbitrarily picked as "ipsilateral." Each ROI's correlation (r) with PCC was calculated and Fisher z-transformed into linear variables. One tailed t-tests determined if ipsilateral ROIs were less correlated with PCC than contralateral ROIs.

Results: The difference of [r(PCC-iHPC) minus r(PCC-cHPC)] was significantly less than 0 for TLE patients ($p=0.042$) but not for control participants ($p=0.714$)(Figure 1). No other default mode component showed this group difference; the difference of [r(PCC-iPAR) minus r(PCC-cPAR)] was not significant for either group (Figure 2), and r(PCC-MPFC) did not differ between groups (not shown). Boxplots for these correlations by group are depicted in Figures 1 and 2; bars, diamonds and circles respectively indicate median, mean, and outlier values.

Conclusions: We report diminished DMN recruitment of HPC in TLE patients. Only one-third of patients presented with MTS, suggesting that diminished HPC recruitment does not solely stem from anatomic irregularities. Our finding of diminished hippocampal connectivity irrespective of hemisphere may stem from our usage of a resting-state task, which we believe is a more ecologically valid measure of DMN functional connectivity than task-related deactivations. Given the absence of hippocampal sclerosis in most of our patients, we believe the reduced PCC-HPC connectivity cannot be attributed to a purely anatomical etiology.

IMAGE: images/900267_A.jpg

Figure 1. Diminished default mode network recruitment of affected vs unaffected hippocampus in patients with unilateral temporal lobe epilepsy. The difference between PCC correlation with iHPC and PCC correlation with cHPC is significantly less than 0 (one-sided t-test, $p<0.044$) for TLE patients but not healthy control participants. Diamonds, bars, and circles respectively indicate means, medians, and outliers.

IMAGE: images/900267_B.jpg

Figure 2. Intact default mode network recruitment of ipsilateral vs. contralateral inferior parietal lobe in patients with temporal lobe epilepsy. Unlike the hippocampus, the correlation of PCC with iPAR minus its correlation with cPAR is not significantly less than 0 for either group.

3.181

OXYGEN-ENHANCED MRI: A NOVEL IMAGING MODALITY FOR THE DIAGNOSIS AND LATERALIZATION OF TEMPORAL LOBE EPILEPSY

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Rationale: To explore the utility of oxygen-enhanced MRI, a novel technique of assessing regional brain metabolism, in a set of normal adult volunteers and temporal lobe epilepsy patients. To assess the sensitivity and specificity of the method in the diagnosis and lateralization of disease in MRI-lesional and nonlesional patients.

Methods: Six right-handed adult normal volunteers and eight right-handed patients with temporal lobe epilepsy were studied. Four patients had lesions concordant with their epilepsy on high-resolution structural MRI. Four patients were nonlesional. Oxygen enhancement

(OE) was carried out by administering 100% O2 in two discrete 5-minute epochs within a 25-minute period, during which T2* (blood oxygen level dependent, BOLD) signal was recorded in continuously acquired gradient-recalled echo-planar images. Data from nine temporal lobe subregions were subjected to spectral analysis and statistical testing.

Results: OE resulted in unambiguous concordant positive T2* signal change in all temporal lobe subregions, in all subjects. Overall BOLD response to OE, assessed by Fourier spectral power peak, was significantly less in patients than normals ($p < 0.025$). This was statistically significant individually in four patients; in two, there was a trend to left-right asymmetry concordant with the laterality of the epilepsy. Analysis of the distribution of spectral power within the temporal lobe revealed significant differences from normals in five patients ($p < 0.01$ in all, corrected for multiple comparisons), concordant with epilepsy laterality in every case. Two of the latter patients were nonlesional on structural MRI.

Conclusions: Echo-planar MRI may be deployed as a metabolic imaging modality by exploiting the effect on the T2* signal of increasing inspired oxygen concentrations. The technique is safe and straightforward, requiring no active patient cooperation. In this small group, it demonstrates apparent high sensitivity (62.5%) and specificity (100%) in the diagnosis and lateralization of hypometabolism associated with lesional and nonlesional temporal lobe epilepsy. Further work with a larger population and other focal epilepsy syndromes will establish OE-MRI's mainstream clinical utility, in particular, its relationship to radioligand-based metabolic imaging (PET) and MR spectroscopy in epilepsy.

3.182

FUNCTIONAL INTEGRITY OF MALFORMATIONS OF CORTICAL DEVELOPMENT IN A LANGUAGE NETWORK: AN FMRI STUDY

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Rationale: Functional reorganization of cerebral cortex occurs in subjects with malformations of cortical development (MCD). In some MCD, functional MRI (fMRI) shows blood oxygen level-dependent (BOLD) activation in malformed cortices, suggesting their functional integrity. This raises concerns about post-surgical deficits in patients with MCD and medically refractory epilepsy. We aimed to assess functional integrity of MCD in language neural network in patients with epilepsy and MCD by use of fMRI.

Methods: Forty-six patients (26w/20m) aged 15-73 years (mean 33.5 years) with MCD and epilepsy were selected at the Department of Neurology and Neurosurgery, Medical University Innsbruck, Austria. All subjects underwent MRI (1.5-T) and fMRI. Single-subject image analysis was performed with statistical parametric mapping (SPM5).

MCD diagnosis was based on MRI and classified according to Barkovich et al., 2005. MCD were located either in vicinity of language cortex - Broca's and Wernicke's areas or subependymally along lateral ventricles.

Patients had to generate silently words staring with letters "K" and "S" and words in categories "Animals" and "Tools".

Patients were tested for the ability to perform the task before scanning. All patients had been seizure free for at least 48 hours prior to fMRI study.

Subsequently, seven patients underwent epilepsy surgery. Histological classification of focal cortical dysplasia (FCD) was based on nomenclature proposed by Palmini et al. 2004.

Results: Fifteen patients had periventricular nodular heterotopias (PNH); nine- polymicrogyria (PMG); five- FCD type II; seven- FCD type I; six- tuberous sclerosis (TS); one- dysembryoplastic neuroepithelial tumour; one - hemimegalencephaly; one - subcortical laminar heterotopia (SLH); and one - TS with PMG.

Majority of patients (44/46) had focal epilepsy; 32/46 (70%) were pharmacoresistant. Mean age at seizure onset was 15 years (range 1-61); mean epilepsy duration for time of fMRI- 12.5 years (range 1-58).

Shift of BOLD activation from MCD affecting language cortex was observed only in patients with FCD type II (3/5) and TS (2/6). Malformed cortices involving language cortex harboured BOLD activation in patients with FCD type I (6/7), PMG (4/10) and SLH (1/2). In PNH situated along lateral ventricles BOLD activation was not observed. In four patients no BOLD activation was registered. Neither shift of BOLD activation from affected language cortices nor their BOLD activation, were influenced by age at seizure onset, seizure frequency during the first year of epilepsy, epilepsy duration, seizure outcome or handedness.

Bilateral BOLD activation of language cortices was observed in 24/46 (52%) patients (either unaffected or dysplastic) irrespective of handedness, age at seizure onset, laterality or type of MCD.

Conclusions: In patients with MCD affecting language cortices, word generation task fMRI suggests functional integration of MCD due to abnormal neuronal migration (SLH) or organization (FCD type I, PMG) and shift of function from MCD due to abnormal neuronal proliferation/apoptosis (FCD type II, TS).

3.183

HIGH-DENSITY EEG SOURCE IMAGING AND CONNECTIVITY ANALYSIS IN PARTIAL EPILEPSY PATIENTS

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Rationale: EEG source imaging is a useful tool to localize epileptogenic foci because of its high temporal resolution at the millisecond scale and its noninvasive nature. A novel ictal source analysis approach was previously developed in our lab for spatial-temporal source localization and connectivity analysis. In this study, we evaluate the ability of the approach to identify epileptogenic foci for high-density EEG recordings in partial epilepsy patients.

Methods: High-density EEG seizure data with 76 channels was recorded in eight medically intractable partial epilepsy patients. All the patients had surgical resections, and were either seizure free or had significant seizure reduction one year after the operation. The EEG sources were modeled as the equivalent current dipoles. Patient-specific boundary element head models were created from their structural MRI. Subspace source imaging method (FINE) was used to localize the ictal sources in the 3-Dimensional brain. Source space connectivity analysis approach was then applied to identify the primary ictal sources. The

results were evaluated by comparing the source locations with surgical resections.

Results: 18 seizures in eight patients were analyzed in this study. Source locations of 11 seizures were within the surgical resection lesions. Source locations of 4 seizures were within 10 mm distance to the lesion boundaries. Sources in the remaining 3 seizures were located in brain areas more than 10 mm away from surgical resection lesions. Source analysis for these eighteen seizures had a mean localization error 4.02 mm and standard deviation 6.93 mm.

Conclusions: High-density EEG source imaging and connectivity analysis approach were applied to study the noninvasive ictal source localization. The source imaging results were well co-localized with the post-operative MRI lesions. Majority of the ictal sources identified were either overlapping with, or close to patient surgical resections. These results suggest the potential application of high-density EEG source imaging in localizing epileptogenic foci for pre-surgical planning.

3.184

DECREASED AMPLITUDE OF LOW FREQUENCY BOLD FLUCTUATIONS IN THALAMIC SUBREGIONS OF PATIENTS WITH IDIOPATHIC GENERALIZED EPILEPSY

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Rationale: Idiopathic generalized epilepsy (IGE) is characterized by widespread cortical hyperexcitability without any detectable cortical or subcortical lesion. The excess neuronal synchrony may result from sodium or GABA channelopathies that alter thalamic activity or thalamo-cortical loops. Recent resting state studies in temporal lobe epilepsy have found disturbances in low frequency fluctuations (LFO) of the blood oxygen level dependent (BOLD) fMRI signal.(Zhang et al. Hum Brain Mapp 2010. Epub ahead of print.) The amplitude of such LFOs, in the range of 0.01-0.08 Hz gives insight into the nature and extent of spontaneous neuronal activity. (Zou et al. Neuroimage. 2010;49(2):1432-45) In the present resting state study, analysis of thalamic subregions was used to characterize regional differences of the amplitude of LFOs in patients with IGE compared to controls.

Methods: Fourteen patients with IGE and 14 age- and sex-matched controls underwent fMRI 3T scans during which they were instructed to close their eyes for the entirety of the 6 min 38 second scan. Analysis of spontaneous BOLD fluctuations was performed with Resting-State fMRI Data Analysis Tool Kit. Images were bandpass-filtered at 0.01-0.08 Hz and co-registered to a common standard template. Within a probalistic mask of the thalamus, fractional amplitude of low frequency fluctuations (fALFF) estimates were generated for each voxel. (Behrens et al. Nat Neurosci. 2003;6(7):750-757) Unpaired t-tests were used to compare the average fALFF of controls and patients of the thalami and thalamic subdivisions.

Results: The average of the fALFF over the entire left thalamus is decreased in IGE patients compared to normal controls. Additionally, we found a significant decrease in fALFF in patients in both left and right thalamic subdivisions that project to the prefrontal cortex. The subdivision on the right that projects to the premotor cortex also showed a statistically significant decrease in fALFF in IGE patients.

Conclusions: Patients with idiopathic generalized epilepsy showed abnormal low-frequency BOLD activity in specific thalamic regions that project to the frontal lobes. These results may explain findings of maximal negative generalized discharges in bifrontal regions and impaired cognitive performance, such as executive functioning in these patients. (Piazzini et al. Epilepsia 2008;49(4):657-62) Disturbances in the spontaneous neuronal activity in the thalamus may account for generalized seizures or allow for seizure propagation in this group of epilepsy patients. In addition, this study shows that inter-ictal resting state fMRI can be used to detect functional abnormalities in patients with IGE while no anatomical abnormalities are identified.

3.185

THE USE OF SPECT IN THE EVALUATION OF EPILEPSY SURGERY IN INFANTS

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Rationale: The routine evaluation for epilepsy surgery often includes SPECT imaging. There are age-dependent changes in physiology that lead to differences in SPECT utility between children and adults. The subset of very young children may be different as well, and has not been previously reported in a sizable cohort.

Methods: We retrospectively summarized all infants who underwent a SPECT injections for epilepsy surgery prior to the age of 1 year. Most children had more than one SPECT, and all available SPECT data was included. Resection completeness was determined using two criteria: EEG/MRI completeness and SPECT completeness. We compared the SPECT findings to outcome data regarding seizure freedom and histopathology.

Results: Thirteen infants underwent SPECT as part of the evaluation for epilepsy surgery. Thirty-two SPECT studies were performed (average of 2.5 SPECT scans per patient). Age at the time of first SPECT varied between 40 days and 354 days. Outcome after the first epilepsy surgery was seizure free in 30% (n=4) and 50% or less seizure reduction in 70% (n=9). Completeness was achieved by both criteria in 15% (n=2) patients; MRI/EEG completeness was present in another 15%, and SPECT completeness alone in another 7% (n=1). None of the patients with incomplete resection by both criteria (n=8) were improved after surgery. Most (80%; n=4) of the complete resections by one or more criteria were seizure free.

Conclusions: The outcome of epilepsy surgery in infants was bimodal, with all subjects either seizure free, or minimally improved (with <= 50% reduction). The completeness of resection was judged by MRI/EEG and SPECT criteria independently, and being complete in either respect was a necessary condition for seizure freedom. This is the first cohort of infants with SPECT data, and although the numbers were too small to compare the criterion of resection completeness, SPECT appears to have a valuable role in the management of infants with intractable epilepsy.

Comparison of resection completeness with epilepsy surgery outcome

IMAGE: tables/909834_T1.jpg

3.186

ISAS INTER-RATER AGREEMENT IS SUPERIOR TO SISCOM AND RAW SPECT ON MEASURES OF LOCALIZATION AND DIAGNOSTIC CONCLUSIVENESS

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Rationale: The value of Ictal-SPECT in the pre-surgical evaluation of epilepsy patients is well established. Among ictal-SPECT processing methods SISCOM (Subtraction Ictal SPECT Coregistered to MRI) is the most widely accepted and extensively validated. However, other approaches such as ISAS (Ictal-Interictal Subtraction Analysis by Statistical Parametric Mapping) offer the objectivity of statistical measures. ISAS derives the statistical significance of a patient's SPECT activity through a voxelwise comparison to pooled and parameterized data from normal subjects. We sought to compare the inter-rater reliability of these two methods to visual analysis of raw SPECT data in terms of localization and study diagnostic conclusiveness.

Methods: Ictal and interictal SPECT scans were obtained from 67 consecutive patients as part of their epilepsy pre-surgical evaluation. These raw scan pairs were each further processed using SISCOM and ISAS methods. A panel of 3 blinded experienced reviewers from different institutions (ALP, KHL, BCO) evaluated each patient's SPECT data in 3 forms; raw unprocessed ictal-interictal pair, with SISCOM processing, and with ISAS processing. Each reviewer was presented scans in a 16 axial slice (4x4) configuration and asked to identify 1) the location of the most significant SPECT activity within one of 30 pre-specified brain regions, and 2) the overall diagnostic conclusiveness of the study judged as "definitely localizing", "probably localizing", or "not localizing." Proportions of inter-rater agreement were calculated, and inter-rater reliability among the 3 reviewers was determined for each of the 3 processing methods using Fleiss' Kappa method.

Results: In our study population, containing 20% temporal lobe and 80% extratemporal localization, the proportion of studies in which all 3 reviewers agreed on the same ROI as containing the most significant activity was RAW = 6% (95% CI, 0.3%-12%), SISCOM = 13% (5-22), and ISAS = 30% (19-40). All 3 reviewers agreed that no single ROI predominated as most significant in 37% (26-49), 22% (12-32), and 7% (1-14) respectively. Studies with total disagreement among all 3 reviewers on the most significant ROI were 9% (2-16), 18% (9-27), and 12% (4-20), respectively. The inter-rater reliability (ê) was 0.36, 0.42, and 0.51 respectively when "not localized" was included as a 31st ROI. The proportion of studies judged by all 3 reviewers as "localized" or "probably localized" was 10% (3-18), 25% (15-36), and 40% (28-52), respectively.

Conclusions: Ictal-interictal SPECT, when processed using the ISAS method, yields better localization agreement, fewer "non-localized" scans, and less reviewer total disagreement, than those with SISCOM processing. SISCOM was shown to be superior to raw scans in most but not all of these same measures. This ISAS>SISCOM>RAW agreement trend was also reflected in the inter-rater reliability (ê) of the three methods. Finally, ISAS tended to more often produce scans judged as diagnostically conclusive, i.e. localizing, than SISCOM, and much more often than raw SPECT.

3.187

MRI DIFFUSION TENSOR IMAGING (DTI) AND MR SPECTROSCOPY (MRS)IN STRUCTURAL NEGATIVE TEMPORAL LOBE EPILEPSY

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Rationale: Hippocampal sclerosis (HS) is the most common pathology of non-lesional temporal lobe epilepsy (NLTLE). Most of them can be detected on a high resolution structural MRI. However, a significant number of patients with NLTLE with EEG and clinically well-lateralized temporal lobe seizures have no evidence of HS on high resolution structural MRI. Diffusion tensor imaging (DTI) can provide information about white matter fiber orientation and integrity. Proton MRS allows detecting early metabolic alterations in the brain even before structural changes. In this study we investigate whether DTI and MRS can provide extra information about hippocampal formation (HF) integrity in structural negative NLTLE.

Methods: We retrospectively analyzed 10 patients with EEG evidence of well-lateralized temporal lobe epilepsy. All patients had high resolution structural MRI, DTI, and MRS. All MRIs were performed in 3T MR Scanner. The standard high resolution structural MRIs were reviewed by a neuroradiologist who was blind to the lateralization of the seizures. Mean diffusion (MD) and fractional anisotropy (FA)were measured from region of interest(ROIs) on anterior HF bilaterally. MRS was performed with single voxel (15mm x 15 mm x 15mm) sampling from anterior HF bilaterally. The MD, FA and NAA/Cr ratio were compared between ipsilateral and contralateral to the epileptogenic zone as determined on the basis of interictal and ictal scalp EEG recordings. Paired samples test was performed in this study. This study was approved by the University of Illinois College of Medicine at Peoria IRB.

Results: There is significant difference in all MD, FA, and NAA/Cr ratio between ipsilateral and contralateral side of HF. In the ipsilateral side to the epileptogenic zone, MD significantly increased (10.47 +/- 1.08 x 10-4 mm2/s vs 9.267 +/- 0.57 x 10-4 mm2/s) ($p = 0.012$); FA significantly decreased (0.124 +/-0.019 vs 0.15 +/- 0.015) ($p = 0.03$); and NAA/Cr ratio significant decreased (1.28 +/- 0.12 vs 1.45 +/- 0.13) ($p = 0.014$).

Conclusions: The results suggest that DTI and MRS could provide complementary information to help identify the HS on structural MRI negative NLTLE. They also suggest that both gray matter and white matter are involved in HS even before it can be detected by high resolution structural MRI.

3.188

"ICTAL" OR "PERI-ICTAL" PET FINDINGS IN PATIENTS WITH REFRACTORY EPILEPSY AND FOCAL CORTICAL DYSPLASIA

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Rationale: To present three patients with refractory epilepsy and "ictal" PET findings corresponding to histologically confirmed focal cortical dysplasias (FCD).

Methods: Patients with focal refractory epilepsy studied with Video-EEG monitoring, brain MRI, and PET with F18-FDG injected immediately after electroclinical seizures.

Case 1: male, 10 months old, left head version seizures since the age of 8 months, 10 seizures per day in average at surgery.

Case 2: female, 28 years old, with complex partial seizures (CPS) since the age of 25, the average seizure frequency was three events per week.

Case 3: male, 3 months old, with focal refractory epilepsy since the 5th life day. Seizure frequency was 6 to 8 per day.

Results: Case 1: MRI: right frontal lesion suggesting FCD. Video-EEG: 12 seizures starting in right frontal region. "Ictal" PET: hypermetabolic area corresponding with MRI lesion (Fig. 1). Surgical resection was guided by intraoperatory ultrasound. Histology: type II-B FCD. Outcome: seizure free at 6-month follow-up.

Case 2: MRI: right hippocampal increased signal, suggesting hippocampal sclerosis. Video-EEG: three electroclinical seizures starting in right mesial temporal region, and several electrographic ictal events in the same area. "Ictal" PET: very well localized right hippocampal hypermetabolism (Fig.2). Histology: type II-B FCD. Outcome: seizure free at 3-month follow-up.

Case 3: MRI suggests right occipital FCD. Video-EEG shows ictal onset on the same area. "Ictal" PET: hypermetabolic area corresponding with MRI and EEG. The histological finding was a FCD type II-B.

Conclusions: Interictal PET is a valuable tool in the pre-surgical evaluation of refractory focal epilepsy. However, ictal abnormalities and its correlation with histological findings and postsurgical outcome have not yet been delineated. In these patients, ictal PET had an excellent correlation with MRI lesions and with seizure onset on video-EEG. Although follow up is not long enough, we suggest ictal PET can be useful at least for FCD cases. Proper implementation requires continuous EEG recording before and during PET study.

For another hand the expression "Ictal PET" could be changed to "Peri-Ictal PET", because the injection with F18-FDG was immediately after the seizure and not during the seizure self.

IMAGE: images/907975_A.jpg

IMAGE: images/907975_B.jpg

3.189

SIMULTANEOUS INTRACRANIAL EEG AND FMRI OF INTERICTAL EPILEPTIC DISCHARGES IN PATIENTS WITH EPILEPSY

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Rationale: Intracranial EEG (icEEG) has much greater sensitivity and spatial resolution than scalp EEG but spatial coverage is limited. We aimed to simultaneously record intracranial EEG and fMRI to study the haemodynamic correlates of localised epileptic icEEG activity both over the whole brain and in local regions where the epileptic activity was recorded from.

Methods: Two patients undergoing presurgical evaluation with icEEG (#1: 76 subdural contacts, #2: 66 subdural contacts and 2x6 contact depth electrodes) were scanned with a 1.5T scanner. We used a head RF-coil, low-SAR sequences (d"0.1W/Kg head-average), and a highly reproducible external electrode cable configuration. Sixty four channels of icEEG was recorded with MR compatible equipment during fMRI. This protocol was specifically safety tested in-vitro with heating <0.1°C. We acquired 2x10min EPI acquisitions (TE/TR40/3000ms 38x2.5mm slices, 0.5mm gap, 3x3mm in-plane resolution) during rest. Standard artefact correction methods were applied to EEG and general linear models containing visually identified interictal epileptiform discharges (IEDs) were applied to the fMRI data. Significant correlations were investigated both over the whole brain and in a-priori defined volumes of interest (VOI) around the most epilpetic contacts.

Results: Direct visual inspection of the cortex upon electrode explantation showed no evidence of adverse effects and histological reports were unremarkable. The corrected intracranial EEG was of good quality and fMRI image quality was sufficient (artefact was dependant on electrode type/location). Significant fMRI changes ($p<0.001$ uncorrected) correlated to IEDs were obtained both local to the IED-contacts and remote from all the implanted electrodes. Highly significant correlations were obtained between IEDs and fMRI signal in apriori defined VOIs. In one case, results showed a network including regions that could not be sampled by icEEG, in agreement with findings from magneto-encephalography and offering some explanation for the persistence of seizures after surgery which only included the icEEG sampled focus.

Conclusions: Under specific tested circumstances, simultaneously icEEG and fMRI can be acquired without adverse health effects in epilepsy patients. Data quality was sufficient to obtain networks associated with IEDs and local coupling between icEEG and fMRI signals. In one patient clinically relevent information was obtained. The simultaneous acquisition of intracranial EEG and fMRI therefore allows the investigation of epileptic activity over a greater range of spatial and temporal scales.

IMAGE: images/907420_A.jpg

Simultaneous EEG-fMRI in 1 patient. Scanner artefact corrected EEG is shown top left. From this IEDs were visually coded. The resulting model revealed two clusters of fMRI changes one close to and one remote from the electrode contacts where IEDs were recorded.

3.190

SEIZURE FOCI IDENTIFICATION: COMPARING FMRI BASED INTRINSIC CONNECTIVITY MAPPING AND SPIKE CORRELATED FMRI

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Rationale: Voxel based measures of intrinsic connectivity contrast (ICC), based on network measures reflect how well each tissue element is connected to all the other tissues in the brain or within a hemisphere. We hypothesized that a novel ICC approach contrasting ipsi-contralateral connectivity could isolate epileptogenic tissue, due to

altered connectivity patterns, in epilepsy patients when they are compared to normal healthy control subjects. This study compares the tissue regions localized with ICC, to regions isolated using simultaneous eeg-fMRI spike localization methods. Such an ICC approach could potentially provide a relatively easy approach for isolating the tissue nodes that lead to seizures in epilepsy patients.

Methods: Simultaneous EEG and fMRI recordings were performed on nine intractable epilepsy patients (age 7-50 yo, mean 29.8 yo, 5 male). A gradient-echo fMRI sequence was used for the fMRI (3T scanner , TR=1550 ms, TE=60 ms, FA=80, 25 slices, FoV=240 mm, base resolution=128). Interictal spikes were read from the preprocessed EEG data, and the timing of spikes (events in an event related analysis) were used to model the fMRI data using the generalized linear model. Seventy five healthy control subjects ages between 18 to 65 were scanned in the resting state using 6 runs of BOLD data, also on a 3T scanner. The ICC measure used a voxel based calculation of the network property "degree" for each voxel in the brain within the same (ipsilateral) hemisphere and subtracted from the contralateral measure of "degree" on a voxel by voxel basis. This ICC difference map was then compared with the spike correlated fMRI map and also with the clinical consensus that was drawn from examining MRI, difference SPECT, PET, EEG, and EEG data that are available for each patient.

Results: In four out of nine patients, the intrinsic connectivity maps had the largest clusters in the same regions as the spike correlated fMRI maps, which also agreed with the clinical impressions. In three other subjects the intrinsic connectivity maps had prominent clusters that coincided with the spike correlated fMRI maps, and which also were in agreement with clinical impressions. The remaining 2 subjects either had poor spike localization or no agreement with the ICC difference map.

Conclusions: Overall, the intrinsic connectivity maps agreed with both the spike correlated fMRI maps and with the clinical impressions. The results suggest that this ICC measure may be a promising tool for epilepsy surgical planning, especially considering that it is non-invasive and possibly can be used for evaluating patients with infrequent or low-amplitude interictal spikes. Further studies with more patients are needed to confirm these promising results.

IMAGE: images/906214_A.jpg

Sample Data from 4 Patients: Top Row: ICC Map (Ipsi-Contra): Single Patient vs Control Subjects. Bottom Row: Spike correlated fMRI. Localization of spike fMRI and ICC measures show excellent agreement.

3.191

TWO METHODS OF FUNCTIONAL CONNECTIVITY IN LANGUAGE COMPREHENSION

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Rationale: Cognitive activities, such as language, require coordinated processing across separate areas of the brain. We examined two fMRI methods of assessing functional connectivity within the language network: ROI-based linear correlation coefficients and individual seed region-based fcMRI analyses.

Methods: 58 typically developing, right-handed children ages 4-12 years (28 boys; mean age=8.8±2.6 yr; mean FSIQ=116±14) underwent 3T EPI BOLD fMRI with an auditory description decision task. Data was analyzed in SPM2 using a region of interest (ROI) approach. Regional laterality indices (LI) for Wernicke's area (WA), inferior frontal gyrus (IFG), and middle frontal gyrus (MFG) were calculated using LI toolbox bootstrap method. Categorical language dominance and mean LI were analyzed; left language dominance for each region was defined as LIe"0.20. For Method 1, individual linear correlation coefficients were computed between pairs of time course signals extracted from the ROIs to determine the degree to which those brain regions fluctuate synchronously during the task. For Method 2, individual variability in functional activation was accounted for by extracting the time series from the subject's peak voxel coordinates within the ROIs to add as regressors in the general linear model task design matrix.

Results: Method 1: Functional connectivity between inter- and intra-hemispheric pairs of language regions was strong did not differ by age ($p>.05$). Age and task accuracy were correlated ($r=0.36$, $p<.01$); controlling for overall accuracy, Left IFG "! Right IFG connectivity was negatively correlated with age ($r=-.27$, $p<.05$). Connectivity between left and right WA was correlated with regional LI in temporal (WA: $r=-.42$, $p=.001$) and frontal regions (IFG: $r=-.34$, $p<.01$; MFG: $r=-.34$, $p<.01$); whereas frontal homologue (IFG, MFG) connectivity correlated only with LI in frontal regions ($p<.05$). Method 2: A priori assumptions of temporally synchronous areas were not required. Areas of activation for all three seed regions included left inferior and middle temporal gyri, left IFG/MFG, and right cerebellum for subjects of all ages. In SPM ANOVAs by age group, the 4-6 year olds showed greater connectivity than the 7-12 year olds with posterior cingulate cortex, right angular gyrus, and left MFG/SFG areas from all three seed regions.

Conclusions: The two methods show that functional connectivity results are dependent on the seed regions chosen and the technique used to extract connectivity values. We found highly synchronous activity between language regions regardless of age. The inter- and intra-hemisphere tracts of functional connectivity appear to be set by an early age (prior to age 4).

3.192

THE EFFECT OF FRONTAL AND TEMPORAL SEIZURE FOCI ON REGIONAL LANGUAGE NETWORKS

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Rationale: Atypical language dominance is frequently identified in patients with focal epilepsy; the effect of seizure focus site within the left hemisphere is not well characterized. We aimed to examine the effect of seizure focus on the expression of regional language laterality by comparing patients with frontal and temporal seizure foci. We further compared the effect of neocortical versus mesial seizure focus in those patients with a temporal focus.

Methods: We studied 90 patients (50 males; mean age 23.3±12.9 years) with left hemisphere focal epilepsy (mean age of onset 11.7 ±8.3 years). 18 patients had a frontal lobe focus, 72 temporal lobe focus (43 mesial; 29 neocortical). Subjects performed an auditory word definition language paradigm using 3T BOLD EPI fMRI. Data was analyzed in SPM2 using a region of interest (ROI) approach. Regional laterality

indices (LI) for inferior frontal gyrus (IFG), and Wernicke's area (WA) were calculated using LI toolbox bootstrap method. Categorical language dominance and mean LI were analyzed.

Results: Mean WA LI was lower for subjects with a mesial temporal focus compared to a frontal focus (p=0.04) and categorically, there was a greater proportion of atypical language in WA for subjects with a mesial temporal focus compared to a frontal focus (÷2=4.37, p=0.04). WA LI did not differ for subjects with a neocortical focus compared to a mesial focus or a frontal focus (p>0.10). Mean IFG LI and proportion of atypical language in IFG were similar across seizure focus groups (p>0.10). Age and age of onset were not correlated with mean laterality in WA or IFG (p>0.10). Epilepsy duration tended to be negatively correlated with WA LI (r=-0.18, p=0.10), but not IFG LI (p=0.38).

Conclusions: Temporal lobe seizure focus appears to have wide-ranging effects on the distributed language system; the effects of a frontal lobe focus are less pronounced on posterior networks.

3.193

MAGNETOENCEPHALOGRAPHY FOR LANGUAGE MAPPING: A NEW APPROACH TO LOCALIZE BOTH LANGUAGE RECEPTIVE AND EXPRESSIVE AREAS

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Rationale: Localizing language receptive (i.e., Wernicke's) area and expressive (i.e.,Broca's) area are crucial for pre-surgical planning in patients with epilepsy and brain tumors, using non-invasive functional imaging techniques, such as Magnetoencephalography (MEG). It has been reported that \ Wernicke's area can be reliably localized using MEG [1]. However, it has been challenging to localize both Wernicke and Broca's areas using one language test with MEG. In the present study, we investigate a new approach of localizing both language receptive and expressive areas with one procedure using MEG.

Methods: Fourteen healthy control subjects and four pre-surgical patients were examined using a new MEG language test. In this approach, language mapping of receptive and expressive language-specific areas was assessed using a word recognition and silent reading task. In this task, four tumor patients were asked to listen toand remember target words first, then recognize and silently read the target words from a mix of the target words and new words. A whole-head MEG system (Elekta/Neuromag VectorView) with 306 channels was used to record the language responses. The MEG data was first run through MaxFilter [2][3] to remove external interferences (e.g., magnetic artifacts due to metal objects, strong cardiac signals, environment noises, etc.), and to correct for head movement. The artifact-free MEG signals were averaged with respect to the onset of the stimuli. The trial-averaged MEG responses were then analyzed using the equivalent-current-dipole (ECD) model in the Elekta/Neuromag software package.

Results: In healthy control subjects and pre-surgical patients, we were able to localize the primary language areas, including Broca's area in the left inferior frontal cortex (Brodmann areas 44 and 45) and Wernicke's area in the posterior aspect of the left superior temporal gyrus. The top row of Fig. 1 shows the language-receptive area in the left hemisphere localized by MEG using the new approach, and the bottom row is for the language expressive area obtained during the same task. Similar result is shown in Fig. 2 for another pre-surgical patient with a right hemisphere lesion.

Conclusions: MEG is a non-invasive functional imaging technique which can localizelanguage-specific areas. Our results show that the word-recognition/ silent reading task can identify the language dominant hemisphere and localize the expressive speech area as well as the receptive-language area in pre-surgical patients.

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PMID: 18196307: 2008.

IMAGE: images/908204_A.jpg

IMAGE: images/908204_B.jpg

3.194

EEG-FMRI WITHOUT EEG: CAN BOLD CHANGES CAUSED BY EPILEPTIC DISCHARGES BE DETECTED WITHOUT RECORDING THE EEG?

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Rationale: EEG-fMRI localizes epileptic activity (EA) with the high spatial resolution of fMRI. However, EEG recording in the scanner is cumbersome and the method cannot detect BOLD changes caused by EA not apparent on scalp EEG. 2D temporal clustering analysis (2D-TCA) is a relatively new fMRI-based EA localization technique that breaks BOLD activity into components based on timing, finding BOLD changes without the help of the EEG. This study is an investigation into the ability of 2D-TCA to detect epileptic activity of various frequency, extent and location.

Methods: fMRI scans containing simulated EA were created by adding a BOLD signal, simulated using values based on current knowledge of BOLD responses to EA, in specific regions of interest (ROIs) in scans from control subject. Simulated spikes consisted of all combinations of the following characteristics: 1, 5, or 10 spikes per 6 minute scan; hemodynamic response function (HRF) amplitudes of 0.5-2% above baseline, in 0.25% increments; ROI sizes of 12, 33, 36, 43, 80, and 53 voxels (each voxel being 5x5x5 mm). In addition to spikes, a single short seizure was simulated by a 5 s event with the above HRF amplitudes in ROIs of 43, 53, and 63 voxels. A total of 756 simulated scans were created, each with 4 ROIs for a total of 3024 forms of simulated BOLD responses. Using these simulated scans, the limits of 2D-TCA, in terms of responses that it can detect, were investigated. A slightly modified version of the 2D-TCA algorithm as developed by Morgan and Gore (Hum Brain Mapp 2009; 30: 3393-405) was used.

Results: 2D-TCA creates a number of components for a given scan. Fig. 1 shows, for various HRF amplitudes, the true positive rate (TPR) associated with that component which best describes the given form of EA, i.e. that component whose activation map has the highest TPR and lowest false positive rate (generally on the order of 0.01). For

reasonable detection, 1 spike/scan is insufficient, while 5 spikes/scan requires an HRF amplitude of 1.5%, 10 spikes/scan 1.25%, and a 5 s event at least 1%. Although 2D-TCA can create components that precisely describe EA with these characteristics, it is important to note that it also creates many other components not associated with the EA, some of which will also create significant activation maps. Fig. 2 is a box plot showing, for scans simulated with an HRF amplitude of 1% or larger, the number of components whose corresponding activation maps contain clusters larger than a range of sizes. Even with a cluster size threshold of 215 voxels (just under the largest simulated ROI), 2 to 9 components still create significant activation that in some cases could be interpreted as arising from EA.

Conclusions: We have demonstrated that 2D-TCA is able to effectively detect some forms of epileptic activity (large enough in amplitude and extent), but it can only be effectively used to validate localization by other means or to create hypotheses as to where this activity may be occurring because it also detects some responses not caused by epileptic discharges.

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IMAGE: images/896174_A.jpg

Fig. 1: TPR for various HRF amplitudes and forms of EA; as 2D-TCA creates a number of components for a given run, the TPR values shown are those associated with that component whose corresponding activation map best described the ROI of the simulated EA.

IMAGE: images/896174_B.jpg

Fig. 2: The number of components whose activation maps have cluster sizes above various threshold levels; only tests using EA simulated with an HRF amplitude of 1% or more was considered; only data for cluster size thresholds bordering the simulated ROI sizes (i.e. 12, 27, 36, 64, 80, 125, 216) are shown.

3.195

ABSENCE SEIZURES IMPAIR ATTENTION AND NETWORK CONNECTIVITY IN CHILDREN

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Rationale: Patients with childhood absence epilepsy (CAE) frequently demonstrate impaired interictal attention despite pharmacological control of their seizures. To date, no study has investigated the brain networks involved in this impairment.

Methods: We tested attentional vigilance in 26 patients and 22 matched controls using the Continuous Performance Task (CPT). Each subject underwent simultaneous 3T fMRI-EEG and behavioral testing. Areas of activation on fMRI during task were correlated with measures of attention and were used as seed regions in a resting functional connectivity analysis.

Results: Relative to controls, patients demonstrated impaired attention on behavioral testing. This impairment correlated with decreased medial frontal activation during CPT. Analysis revealed an overall trend towards decreased resting functional connectivity between areas of task activation in patients relative to controls. Patients demonstrated significantly impaired connectivity between the right anterior insula/frontal operculum and medial frontal lobes (p=0.016).

Conclusions: CAE patients demonstrate impaired attention on behavioral testing, and our fMRI results reveal disruption in an attention network comprised of an anterior insula/frontal operculum and medial frontal cortex. These findings provide an anatomical and functional origin for interictal impaired attention in CAE, which could potentially lead to treatments targeting these networks.

3.196

FACTORS INFLUENCING ICTAL SPECT FINDINGS IN CHILDREN WITH FOCAL CORTICAL DYSPLASIA

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Rationale: Ictal single-photon emission computed tomography (SPECT) could localize the seizure onset zone in patients with focal cortical dysplasia (FCD) and intractable epilepsy. The aim of our study was to analyze whether parameters of injected epileptic seizures (times of the radionuclide administration, durations, types and ictal EEG patterns of seizures) predict ictal SPECT findings in pediatric FCD cases. The study was conducted on a large population of pediatric epilepsy surgery patients with histologically proven FCD.

Methods: We visually evaluated 98 ictal SPECT studies in 69 children with FCD who underwent excisional epilepsy surgery at the Miami Children's Hospital. SPECT findings were classified as "non-localized", "well-localized" (confined to a region of one gyrus or two contiguous gyri), "lobar" and "extensive" (multilobar or hemispheric) and compared with injection times, types, durations and scalp EEG patterns of injected seizures. Seizures were classified as "simple partial", "complex partial" and "secondarily generalized" and EEG ictal patterns as "localized", "widespread" (multilobar or hemispheric) and "non-lateralized". Relationship among two categorical parameters (types of seizures and EEG patterns) and SPECT findings were evaluated by Pearson Chi-square tests. Parameters measured in seconds (injection times and seizure durations) and their relationship with SPECT findings were calculated by One-way ANOVA and Kruskal-Wallis test. Data were evaluated in three sets: (1) All studies; (2) Studies in previously non-operated patients and (3) Cases that had postsurgical ictal SPECT.

Results: There were 67 ictal SPECT studies in previously non-operated patients and 31 postsurgical scans in subjects before reoperation. 27 ictal SPECT scans were nonlocalized, 19 well-localized, 25 lobar and 27 extensive. SPECT findings were not significantly influenced by injection times (p=0.3094), types of injected seizures (p=0.9152) and their scalp EEG patterns (p=0.3258). Seizure duration significantly influenced extent of SPECT findings: Shorter seizures were associated with localized and longer ones with extensive hyperperfusions. This association was proven in all SPECT studies (p=0.0033) and in studies in previously non-operated patients (p=0.0035), but not in postsurgical SPECT scans (p=0.6538).

Conclusions: Duration of injected seizures significantly influence ictal SPECT findings and may affect surgical planning in FCD patients. However, we failed to prove this relationship in previously operated patients who had postsurgical ictal SPECT scan. Injection times, types

and scalp EEG patterns of injected seizures appeared non-significant in our series.

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3.197

DYNAMIC IMAGING OF COHERENT SOURCES IN ABSENCES AND GENERALIZED PHOTOPAROXYSMAL RESPONSES - A COMPARISON WITH EEG-FMRI STUDIES

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Rationale: Combined functional magnetic resonance imaging (fMRI) and EEG recordings allow to map brain areas involved during generation and propagation of epileptic activity. However, EEG-fMRI is a challenging technique (EEG recording inside the scanner, removing of scanner and pulse artifacts in the EEG, complex statistical fMRI analyses) and is often characterized by an insufficient sensitivity. Dynamic imaging of coherent sources (DICS) is a technique which only involves the EEG: DICS allows to study neuronal interactions by imaging power and coherence estimates using a spatial filter (Gross et al. PNAS 98(2):694-9, Muthuraman et al. IEEE, 2008:4716-9). The aim of this study was to apply DICS to different types of generalized epileptiform discharges, namely absences and photoparoxysmal responses (PPR) and compare it to the EEG-fMRI results obtained from the same data sets.

Methods: Artifact corrected 32 channel EEG recordings (EEG-fMRI data sets 3T MRI) from 10 patients with absences and 7 patients with PPR during the scanning were selected; 6 patients with absences and 6 patients with PPR have been described in previous EEG-fMRI studies (Moeller et al. Epilepsia 2008; 49(9):1510-9, Moeller et al. Neuroimage 2009;48(4):682-95.). For all absences and PPRs the normalised parametric power maps in the 2-5 Hz frequency range were computed to identify the area in the brain with the strongest power. This area was defined as a reference region. The coherence between the reference region and the entire brain was computed for every patient using DICS. In a second step grand averages were computed for a) all absences and b) all PPRs.

Results: Both analyses of single absences and grand average of all absences detected the source area of strongest oscillatory activity in the 2-5 Hz frequency range in the medial frontal cortex. Coherent sources with this reference region were found bilaterally in the frontal and parietal cortex, in the thalamus and in the cerebellum (figure 1). The cortical sources and the source in the thalamus were concordant with the results of the EEG-fMRI group analysis (Moeller et al. Epilepsia 2008). For PPRs the source area of strongest oscillatory activity in the 2-5 Hz frequency range was found bilaterally in the visual cortex for single subjects and in the grand average analysis. Coherent sources with these reference regions were found bilaterally adjacent to the intraparietal cortex, in the fronto-polar cortex and in the premotor cortex. No sources in the thalamus were detected (figure 2). Sources adjacent to the intraparietal sulcus and in the premotor cortex corresponded well with results from the EEG-fMRI analysis (Moeller et al. Neuroimage 2009)

Conclusions: The EEG alone provides information about networks associated with absences and PPRs which is similar to EEG-fMRI results: DICS is able to find coherent sources in the 2-5 Hz range in areas detected by EEG-fMRI. Although both EEG patterns are generalized, only absences show a thalamic involvement, while PPR seems to be a cortical phenomenon.

IMAGE: images/905886_A.jpg

Figure 1 Grand average for all absences: the first source represents the strongest source in the 2-5 Hz range. Sources 2 to 6 show coherence with the first source.

IMAGE: images/905886_B.jpg

Figure 2 Grand average for all PPRs: the first source represents the strongest source in the 2-5 Hz range. Sources 2 to 4 show coherence with the first source.

3.198

CROSS HIPPOCAMPAL INFLUENCE IN TLE MEASURED BY FMRI WITH GRANGER CAUSALITY

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Rationale: The direction and magnitude of interaction between brain regions can be quantified using functional MRI with Granger causality measures of temporal precedence. In this work we use these measures to determine influence between left and right mesial temporal regions in temporal lobe epilepsy (TLE) at rest. We hypothesize that these measures will reflect the order of seizure propagation proposed theories ictal networks of TLE, and may differentiate left TLE from right TLE.

Methods: We acquired high temporal resolution fMRI images of TLE patients as part of a larger study involving lower temporal resolution fMRI. Images were acquired using a Philips Achieva 3T MRI scanner (Philips Healthcare, Inc., Best, Netherlands). The imaging series consisted of a T1-weighted structural MRI image, two low temporal resolution fMRI image sets (64x64, FOV = 240 mm, axial slices, TE = 35 ms, TR = 2 sec, 30 slices, 5 mm thick, 300 dynamics), and one high temporal resolution fMRI image set (same except TR = 500 ms, 9 slices, 400 dynamics). Conventional preprocessing and spatial normalization was performed. (1) Regions of interest (ROIs) - anatomic ROIs were determined using the left and right hippocampus regions of the Harvard Oxford probabilistic brain atlas. Functional ROIs were determined in the left and right mesial temporal lobes using 2dTCA [1] and functional connectivity [2]. These regions were part of a network of increased fMRI activity interictally in 4 left TLE subjects using low temporal resolution fMRI (TR=2s). (2) Region of interest identified in 500 ms TR data - The 500 ms TR data of 10 subjects (2 from functional ROI determination) lateralized by interictal and ictal scalp EEG/video monitoring (1 patient had normal EEG) was spatially normalized to the ROI templates. The average time course in each region was calculated for each subject. (3) Granger causality analysis - An order 1 autoregressive model was used to estimate model parameters for influence of previous time points of left ROI on current time point of right ROI (Influence LEFT), and vice versa (Influence RIGHT) for each patient. Motion parameters were used as confounds. The Influence LEFT-Influence RIGHT measures were then calculated.

Results: We found a large variation of fMRI causality between the left and right TLE patients using the anatomic ROIs (Figure 1a), but a distinct separation between the two groups using the functional ROIs (Figure 1b). Presence of HS and PET hypometabolism was variable in these 10 subjects and not correlated with the fMRI causality measure. One patient in each TLE group was left handed.

Conclusions: These results show that functional MRI with Granger causality can determine differences in cross hippocampal influence between left and right TLE patients if measured using functionally derived ROIs. Further interpretation and correlation to clinical measures are required.

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IMAGE: images/906046_A.jpg

3.199

LATERALITY OF THE EEG-FMRI SEEDED FUNCTIONAL CONNECTIVITY AS A PREDICTOR OF THE SURGICAL OUTCOME OF EPILEPSY

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Rationale: Although the success rate of epilepsy surgery is high (60-80% of medial temporal lobe resection results in seizure freedom), the surgery incurs risk of infection and declining cognitive abilities. Therefore, it is important to assess the possible success of surgery. In the current research, we tested a hypothesis that patients whose functional connectivity from the affected area spreads more bilaterally have lower chances of becoming seizure-free. Three different seed selection methods for computing the functional connectivities were compared.

Methods: Nine intractable epilepsy patients (age: 15-50, mean 36, 5 males) underwent simultaneous EEG-fMRI recording before surgery. Functional MRI (fMRI) images were acquired in four to eight, six-minute scans from each patient using a 3T scanner. EEG (32 channel, 1 kHz sampling) was recorded during the fMRI runs, using carbon fiber electrodes and an anti-polarization EEG amplifier. Patients without seizures followed for at least for 6 months after surgery were deemed seizure-free. Fourteen healthy control subjects (age: 22-34, mean 26, 7 males) also participated in the study.

Three different types of seeds were compared, namely (1) EEG-fMRI seed: based on interictal spike-correlated fMRI activation (2) planned resection area based seeds: planned resection regions specified using Yale Brodmann atlas (3) actual resection area based seeds: the difference images between the pre- and post- surgical anatomical MRI's. When the spike correlated fMRI analysis resulted in multiple clusters, the cluster that overlapped most with the planned resection area was chosen. The laterality indices were computed based on the numbers of suprathreshold voxels in the ipsi- and contra-lateral hemispheres in the connectivity map. Corresponding laterality indices from the controls (using the same seed areas as the patients) were subtracted to yield control-subtracted laterality indices.

Results: The control-subtracted laterality indices computed from the EEG-fMRI seed were significantly lower in the seizure-recurrence group than in the seizure-free group (unequal variance t-test, $t=2.39$, $df=3.92$, $p<0.05$). Neither the planned resection area based laterality ($t=1.84$, $df=4.61$, $p>0.05$) nor actual resection area based laterality ($t=1.90$, $df=5.58$, $p>0.05$) did not differ significantly between the two groups. This may be because the EEG-fMRI based seed captures more spike related fMRI variance compared to resection area based seeds, which are structural in nature. However, there may also be a possible effect of the seed size, as the EEG-fMRI based seeds had smaller area sizes (mean 33.0 voxels, std (standard deviation) 23.7 voxels, voxelsize = 3.4x3.4x5 mm) compared to planned resection area based seeds (mean 3260 voxels, std 2550) or actual resection area based seeds (mean 283 voxels, std 245).

Conclusions: We conclude that the low laterality of the functional connectivity computed from the spike-correlated fMRI seed is a predictor of unsuccessful surgery. A larger scale study is currently underway.

3.200

FUNCTIONAL CONNECTIVITY ANALYSIS OF MEMORY NETWORKS IN EPILEPSY

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Rationale: Functional MRI (fMRI) has been established as a clinically useful tool. In particular, fMRI has proved to be a reliable tool for identifying sensory-motor regions and localizing language. Implementing a clinical memory paradigm for evaluation of mesial temporal function with robust results in individual patients has proven to be more challenging. Functional connectivity MRI (fcMRI) an analysis technique based on task-free resting state fMRI recording — is an alternative approach for mapping functionally related areas of the brain. Potentially, it can be useful in assessing disruption of connectivity in certain disease states, including memory disruption in epileptic patients with hippocampal sclerosis (Frings L et al.2009). We explore the possibility of using connectivity analysis for accessing networks implicated in memory function.

Methods: During the 8 min resting state fMRI scan the subjects were instructed to relax and rest while keeping their eyes closed. Siemens (Erlangen, Germany) system, 3-Tesla (Trio) scanner was used for imaging (EPIBOLD sequence, TE=30ms, flip angle = 90°). Analysis was performed using 1000 Functional Connectomes Project scripts based on AFNI and FSL software packages. We retrospectively analyzed connectivity patterns in five healthy control subjects (ages 11 to 15) and compared these to results in two patient (age 18 and 5) with memory disruption and epilepsy due to hippocampal sclerosis. Resting state data were analyzed for connectivity with ventral precuneus (Vincent JL 2006) and retrospenial (Greicius MD 2009)cortex.

Results: The figure shows connectivity patterns for ventral precuneus seed (MNI coordinates: 0, -60, 24) in one control subject and in one patient. We observed robust connectivity of this seed point with fusiform gyri, parahippocampus and hippocampus. Connectivity pattern was found to be bilateral and symmetric in control subjects, (Fig 1A), which is in agreements with literature reports. In contrast, results observed in an epileptic patients with left hippocampal sclerosis exhibited an asymmetric pattern of connectivity (Fig1B). Connectivity is decreased on the left hemisphere and appears most asymmetric in the hippocampal and parahippocampal regions.

Conclusions: Connectivity in memory networks revealed with fcMRI analysis is bilateral and symmetric in control subjects. This finding appears to be sufficiently robust, so that connectivity patterns can be assessed in individual subjects. Observation in two epileptic patients

with hippocampal sclerosis revealed a deviation from the typical connectivity pattern with diminished connectivity on the side ipsilateral to the MTS. We intend to collect the data in several such patients and study the relationship between the connectivity patterns, the extent and localization of hippocampal sclerosis and the degree of memory function disruption, as assessed by neuropsychological testing.

IMAGE: images/907185_A.jpg

A. CONTROL (top images) B. Patient (bottom images)

3.201

BASAL GANGLIA AND DEFAULT MODE NETWORKS IN EPILEPSY

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Rationale: Spike-triggered EEG-fMRI studies show that epileptic activity may affect brain areas well beyond the epileptogenic cortex, including areas that are engaged in the "default mode network" (DMN) (Gotman, Epilepsia, 2008). A functional brain connectivity study using functional magnetic resonance imaging (fMRI) was performed to find DMN differences between patients with epilepsy and healthy volunteers.

Methods: Ten healthy volunteers and twenty-four epileptic patients (14 with extra-temporal and 10 with temporal epilepsy) participated in the study. Resting state fMRI data, acquired with no explicit task, were obtained using the 1.5 T Siemens Magnetom Symphony scanner. Three hundred scans were obtained from the healthy volunteers, and two runs of 300 or 400 scans were obtained from the epileptic patients. For each subject, an independent component analysis (ICA) was used to separate the BOLD signal into spatially independent components, using the Group ICA of fMRI Toolbox (GIFT) program. In the ICA approach, one or several independent components could be related to epileptic activity anywhere in the brain, independent of the occurrence of spikes on the scalp. The component representing the DMN was chosen according to a spatial correlation with a mask typical for DMN (included in the GIFT program). A second-level analysis was calculated to evaluate differences among the DMN components in the healthy volunteers, patients with temporal epilepsy, and patients with extra-temporal epilepsy using SPM software.

Results: In healthy subjects, the basal ganglia were functionally negatively correlated with typical DMN regions, such as the posterior medial and prefrontal cortices. This negative correlation was significantly lower in the two groups of patients with temporal and extra-temporal epilepsy.

Conclusions: Unlike in healthy subjects, in epileptic patients the basal ganglia are not correlated with a DMN component. This may be interpreted as a sign of an altered or modified function of the basal ganglia in epilepsy.

3.202

CANNABINOID TYPE 1 (CB_1) RECEPTOR BINDING IMAGED *IN VIVO* USING THE PET LIGAND [^{11}C]MEPPEP.

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Rationale: The cannabinoid CB_1 receptor is one of the most abundant G protein-coupled receptors in the brain[1]. Animal models have demonstrated alterations in CB_1 receptor availability in response to seizures. Cannabinoid agonists can have a marked anti-seizure effect in some patients[2]. However, *in vivo* human evidence of cannabinoid receptor alterations in epilepsy is lacking. MePPEP is a novel CB_1 inverse agonist that has been labelled with ^{11}C for use in positron emission tomography (PET). Here we compared post-ictal binding of [^{11}C]MePPEP in two patients to that of controls.

Methods: [^{11}C]MePPEP PET scans were performed in fourteen healthy controls (10 males, mean age 31 years; range 20-65 years) and in two patients (both males, age 29 and 37) with focal epilepsy within two days following a spontaneous seizure presumed to arise either in the temporal or frontal neocortex. All subjects had a 90-minute dynamic PET scan on a Siemens/ECAT 962 scanner, each after intravenous injection of approximately 370MBq (mean: 360MBq, range 316-385MBq) of [^{11}C]MePPEP. Data were motion-corrected with a frame-to-frame co-registration method and spatially aligned with T1-weighted structural 3D images[3] in all controls. Volumes-of-distribution (V_T) were quantified using arterial input functions (IFs) in anatomically defined selected areas[4]. We calculated the global intensities (GI) in all controls and chose hippocampus and inferior frontal gyrus (IFG) as regions-of-interest (ROI) for quantifying V_T. Finally, we compared the uptake of [^{11}C]MePPEP in patients with that of controls using Statistical Parametric Mapping (SPM).

Results: Mean GI of summed 0-90 minute (ADD) images in controls was 1.31 (range 0.8-2.1). V_Ts were generated from three-tissue two-compartment models in both ROIs. Mean V_T value for hippocampus was 17.4 (range 2-6) and for IFG was 7.8 (range 2-16).

Both patients showed upregulation of [^{11}C]MePPEP fixation in the presumed epileptogenic lobe. This was seen on both visual inspection of ADDs and on their preliminary SPM analysis (Figure 1).

Conclusions: Our preliminary *in vivo* findings support a role of G-protein coupled CB_1 receptor in the modulation of seizure activity in humans, and open opportunities for a range of applications for [^{11}C]MePPEP PET as a tool in the presurgical investigation[5]. These results require further validation in a larger dataset of paired inter-ictal and post-ictal studies with data quantified using compartmental models[6] and semiquantitative analysis using SPM.

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IMAGE: images/907088_A.jpg

Figure 1. Statistical Parametric Maps (SPM) analysis of PET data showing clusters of increased MePPEP uptake in the presumed epileptogenic lobe. (A) Images from a patient with frontal lobe epilepsy (cluster p value = 0.076). (B) Images from a patient with temporal lobe epilepsy (cluster p value = 0.006). Colour bars, t scores.

3.203

META-ANALYTIC CONNECTIVITY MODELING OF MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Chronic epilepsy, when unsuccessfully managed, causes significant neurological changes. In addition to the seizure focus, primary epileptogenic cortex may have a noxious effect on more distal brain regions. Evidence suggests that structural alterations occur along neural pathways remote from the seizure focus. Research on functional connectivity in mTLE has shown distinct changes in neural networks, suggesting possible neuropathophysiological underpinnings to this disorder which can only be detected using network-based analysis methods. However, these methods are prone to bias, limiting their generalizability and applicability. Here we use meta-analytic connectivity modeling to develop robust models independent of task and ROI selection for future connectivity analyses.

Methods: We used PubMed to compile a database of papers relating to the structural deficits in mTLE as determined by voxel-based morphometry (VBM). We included papers that met the following criteria: whole-brain VBM analyses implemented,coordinates reported in standard space,studies involving adult, pre-lobotomy patients, and papers written in English. Additional papers were added that were identified in a review by Keller and colleagues(2008). A total of 14 papers were initially identified.

Activation Likelihood Estimation (ALE) Voxel-Based Morphometry Meta-Analysis. We used ALE to determine distal brain regions that exhibited structural deficits in mTLE patients. After identifying the total number of coordinates reported in each of the 14 papers, we excluded those papers reporting 35 or less coordinates. Six papers met this criterion to be included in the analysis. The focus of the main structural deficit cluster within the hippocampus was identified (24,-36,0).

ALE Functional Neuroimaging Meta-Analysis. To examine the functional connectivity of the cluster center from the VBM meta-analysis, we drew a 10mm cube around the coordinate within the hippocampus and seeded the BrainMap database to search for all studies that reported activation within the ROI boundary. Whole-brain coordinates of activations were downloaded. The search produced 42 papers reporting activation within the hippocampal ROI. Taken together, these data propose a model of temporal lobe epilepsy that accounts for both functional and structural deficits.

Results: Consistent structural deficits in the hippocampus, insula, fusiform gyrus, anterior cingulate, parahippocampus, thalamus and mid-occipital gyrus were identified. Functional connectivity was demonstrated in bilateral parahippocampal gyri, superior temporal gyri, precentral gyri, insula, and putamen. Other regions of functional coherence included the thalamus, red nucleus, substantia nigra, right amygdala, anterior cingulate, and lingual gyrus.

Conclusions: The present study used ALE meta-analysis driven connectivity methods to develop a model of temporal lobe epilepsy inclusive of both structural and functional observations. The model holds promise in identifying previously undetected network deficits by capitalizing on the robustness of MACM.

IMAGE: images/906804_A.jpg

3.204

IMAGING CORTICAL NETWORKS INVOLVED IN PREICTAL AND ICTAL CHILDHOOD ABSENCE EPILEPSY WITH MAGNETOENCEPHALOGRAPHY

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Rationale: Childhood absence epilepsy (CAE) is characterized by EEG recordings of generalized, bilaterally synchronous 3 - 4 Hz spike and wave discharges (SWD) concurrent with behavioral arrest and loss of awareness. Recent EEG/fMRI studies in humans and in rats support a model in which SWDs arise from specific cortical foci, rather than occurring as a generalized phenomenon. Here we used magnetoencephalography (MEG) to identify the specific cortical regions active prior to and during absence seizures.

Methods: Using simultaneous MEG and EEG measurements, we recorded absence seizures at 600 Hz from one 5 y/o and one 14 y/o female subject, and two 7 y/o male subjects, all of whom were recently diagnosed with CAE. Recordings were performed before treatment. Spontaneous SWDs were recorded during 0.5 - 2 hr period of data capture. Spectrograms and synthetic aperture magnetometry (SAM) were used to quantify preictal and ictal activity and their corresponding brain loci. SAM was conducted from 0.5 to 50 Hz in 500 ms increments starting 2 s prior to the seizure onset and ending 3 s after the seizure onset. The corresponding activation maps were coregistered with each subject's structural MRI.

Results: Spectrograms revealed broad increases in ictal power over baseline conditions in the MEG sensors from 0-50 Hz with the onset of the first SWD spike, with the greatest power evident in frontal sensors. Up to 2 s prior to the onset of the seizure, SAM revealed significant activations (defined as activity different from baseline with all p's < 0.05) in the inferior frontal gyrus (3 of 4 subjects), middle (3 of 4) and superior (3 of 4) temporal gyri, and precentral gyrus (3 of 4). At the start of the seizure, all subjects exhibited strong activity in the middle frontal gyrus and 3 of 4 subjects demonstrated prominent activity in the superior and inferior frontal gyri, as well as the precentral gyri.

Conclusions: Prior to seizure onset, significant biomagnetic activity was revealed in the frontal, temporal, and precentral gyri. At the start of the seizure, a transition occurred in which frontal activity predominated, with lesser activations evident in the precentral gyri. These results collectively demonstrate a progression of concurrent synchronous activity in the temporal and precentral loci prior to SWD, which leads to frontal cortical activation that occurs with absence seizures. Our results suggest that CAE is a disorder involving a cortical network that first facilitates the onset of SWD, then transitions to SWD discharges affecting a more extended cortical network.

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COREGISTRATION OF MAGNETOENCEPHALOGRAPHY(MEG) AND SUBTRACTION ICTAL SPECT COREGISTERED TO MRI(SISCOM) IN PLANNING FOR EPILEPSY SURGERY

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Rationale: The purpose of this study was to assess if in cases in which the traditional presurgical diagnostic evaluation of continuous video-EEG monitoring, neuropsychological testing, and high resolution MRI does not provide a clear surgical target, completion of both MEG and SISCOM adds complementary localizing information to aid in epilepsy surgery planning compared to either of these modalities alone.

Methods: All consecutive presurgical cases at our epilepsy center between 2007 and 2009 undergoing both MEG and SISCOM were included in this study. A total of twelve cases had complete datasets for analysis. Spontaneous MEG data was acquired and analyzed using a Neuromag system. SISCOM data was evaluated with Analyze software which was also used to coregister MEG and SISCOM. The coregistered data were visually inspected for degree of overlap and classified as either concordant or discordant. Concordant results were further classified as lobar or sublobar.

Results: Of the twelve cases, five were concordant in terms of MEG and SISCOM results. Four of the five of these had underlying cortical dysplasia. The fifth case was nonlesional. Of the four concordant dysplasia cases, two were initially felt to be nonlesional after completion of the traditional evaluation. After the subsequent finding of concordant MEG and SISCOM at a sublobar level however, further analysis of MRI data revealed findings consistent with cortical dysplasia that was not initially identified. In one of these cases re-analysis of the original MRI showed a highly focal area of abnormal cortical thickening by visual inspection as well as cortical thickness analysis with Freesurfer software and later confirmed by pathology. In the other case, a high field, high resolution MRI was subsequently completed and revealed findings consistent with cortical dysplasia that was not seen with prior conventional MRI. Analysis of the single, nonlesional concordant case also showed agreement at a sublobar level. In this case however, a second more subtle area of abnormality was seen on SISCOM that did not have a MEG correlate. Because this more subtle region seen only on SISCOM correlated with the semiology of the patient's seizures, and SISCOM is a measure of ictal activity, while MEG is typically interictal, it was felt that the more obvious area of MEG and SISCOM concordance in this case represented a false positive.

Conclusions: While previous studies have shown that both MEG and SISCOM can independently aid in the placement of intracranial electrodes in epilepsy surgery, this case series suggests that the use of both modalities together may further improve presurgical planning by the identification of structural lesions in select cases that may otherwise be considered nonlesional. As the single false positive case illustrates however, careful analysis of traditional diagnostic test results along with both MEG and SISCOM data and an understanding of the limitations of each is required to avoid mistaking an irritative lesion for an epileptogenic lesion.

3.206

THALAMIC NUCLEI INVOLVEMENT IN SECONDARY GENERALIZED SEIZURES: A SISCOM STUDY

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Rationale: Thalamic relay nuclei receive input from numerous pathways and reciprocate with complex cortical projections; thereby serving as important propagation centers for seizures. We reported blood flow increases in the thalamus in secondarily generalized tonic-clonic (SGTC) seizures by subtraction ictal SPECT co-registered to MRI (SISCOM). Recent studies have shown efficacy of deep brain stimulation of the anterior nuclei of the thalamus in the treatment of refractory epilepsy patients. The aim of this study is to investigate the relationship between thalamic ictal SPECT hyperperfusion and seizure type.

Methods: We previously reviewed all SISCOM data from the Medical College of Georgia from 1998 to 2009. We selected a cohort of SISCOM studies which included only thalamic hyperperfusion. Using Analyze 8.1 (Mayo BIR, Rochester, MN), we reviewed coronal, axial, and sagittal images. Based upon the relationship to the third ventricle, lateral ventricles, and basal ganglia, we identified ictal hyperperfusion in three thalamic regions: the anterior, medial-dorsal, and lateral regions. Using Chi-square test, we analyzed the frequency of thalamic hyperperfusion in SGTC and complex partial (CP) seizures.

Results: We reviewed 128 cases: 76 cases of CP seizures and 52 cases of SGTC seizures. Among the CP seizure cases, there was greater frequency of medial-dorsal thalamic hyperperfusion (42%, 32/76) as compared to anterior (20%, 15/76), or lateral (38%, 29/76) thalamic hyperperfusion. Among the SGTC seizure cases, there was a greater frequency of lateral thalamic hyperperfusion (40%, 21/52) as compared to anterior (25%, 13/52), or medial-dorsal (35%, 18/52) thalamic hyperperfusion; the relationship between regional thalamic hyperperfusion and seizure type was statistically non-significant (Chi-Squire statistics=0.87, Degree of freedom=2, and p=0.64). A second analysis investigated the relationship between the side of thalamic hyperperfusion, and the side of seizure onset. Among CP seizure cases, thalamic hyperperfusion was contralateral to the side of seizure onset in 44/76 (58%) cases; among SGTC cases, thalamic hyperperfusion was contralateral to the side of seizure onset in 33/52 (63%) cases; the relationship between lateralization of thalamic hyperperfusion and seizure type was statistically non-significant (Chi-Squire statistics=0.40, Degree of freedom=1, and p=0.52).

Conclusions: Multiple thalamic regions are involved in CPS and SGTC seizures. Our study indicates that CP and SGTC seizures do not have distinct regional patterns of ictal thalamic hyperperfusion. More investigation is warranted including investigating the relationship between time of SPECT injection and region of thalamic hyperperfusion. This would help to further delineate the subcortical network involved with CP and SGTC seizures.

3.207

PREPROCESSING OF MAGNETOENCEPHALOGRAPHIC DATA IN EVALUATION OF LANGUAGE LATERALIZATION

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Rationale: Magnetoencephalogrephy (MEG) is useful tool for evaluation of language lateralization in patients with epilepsy. Since

language activities are very small on MEG, the data is often distorted by artifacts caused by muscle and eye movements. Recently, temporally-extended signal space separation (tSSS) has been introduced for removing these artifacts. We assessed the usefulness of preprocessing of language MEG data, comparing with the result of WADA test in patients of epilepsy.

Methods: Ten patients with epilepsy had MEG for language lateralization in presurgical evaluation. They also had a WADA test, which showed left language predominance in all patients. MEG data was recorded with a 306-channel whole-head system. The sampling rate was 600Hz. In all patients, we obtained anatomical MRI (magnetization-prepared rapid acquisition gradient-echo: MPRAGE) with a high-resolution 3T scanner. Patients performed a semantic language task for the paradigm of language testing. Serious of words were visually presented on the screen one at a time, and the task was to decide the word is representing abstract or concrete entity. For preprocessing, we processed MEG data with tSSS (Taulu et al., 2004) .In this method, the recored magnetic signals are decomposed into separate components representing both the neuromagnetic signals arising from inside a volume enclosed by the sensor array and any external interference signals arising from outside of the array. For determining language lateralization, we averaged the MEG data by using the timing of word presentation as a trigger. Dynamic statistical parametric maps of language activity were obtained based on a distributed source model (Dale et al., 2000). These maps were projected on the cortical surface derived from each patient's MRI. The activation between 250ms and 550ms after the trigger was analyzed. We calculated laterality index (LI) for each patient by using activation in superior temporal, middle temporal, supramarginal and inferior parietal cortices on both hemispheres. The LI was obtained by LI = (L-R)/(L+R), where L and R is the number of unit dipoles with an F value higher than the threshold value in these cortical areas of left and right hemisphere, respectively. Language predominance was determined based on the LI as follows; e"0.1:left, 0.1>LI>-0.1; bilateral, d"-0.1; Right. We calculated LI from the original MEG data, and tSSS-processed data separately, and compared these result with WADA test.

Results: LI derived from the original data showed the language predominance on the left, bilateral and the right in six, two and two patients, respectively. The LI ranged from -0.51 to 0.63. In contrast, LI of all patients showed left language lateralization. LI of the patients ranged from 0.10 to 0.37.

Conclusions: In our patients, LI derived from tSSS-processed data was more consistent with the language lateralization determined by WADA test than LI obtained from the non-processed data. Preprocessing of MEG data with tSSS may be highly useful for obtaining reliable language lateralization by using MEG.

3.208

METABOTROPIC GLUTAMATE RECEPTOR TYPE 5 (MGLUR5) AND VERBAL MEMORY PERFORMANCE IN MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Abnormalities in mGLUR5, a post-synaptic glutamatergic receptor involved in memory consolidation, have been described in mesial temporal lobe epilepsy (MTLE). Whilst suggesting a role for this receptor in the epileptogenic process, little is known about the extent to which mGLUR5 function contributes to memory deficits associated with MTLE. Here we report the relationship between hippocampal [11C]ABP688 PET binding potential (BP) and performance on a verbal learning and memory task. We hypothesize that decreases in left (dominant) hippocampus BP will be correlated with poorer verbal memory performance in MTLE patients.

Methods: We studied 15 right-handed patients classified into left (n=6) or right MTLE based on interictal/ictal EEG and visual hippocampal analysis in clinical MRI scans. [11C]ABP688 PET scans consisted of a 1 hour dynamic acquisition, with image reconstruction using filter-back projection and coregistration to each patient's MRI. BP maps were generated using a simplified reference tissue method with the cerebellum as reference region. Individual patient MRIs and BP maps were resampled to standard space. Volumes of interest were manually drawn and used for extraction of mean BP within the hippocampal head, the segment in which the most significant abnormalities are seen in epileptogenic hippocampi. All patients were administered the Rey Auditory Verbal Learning Test (RAVLT) as part of the routine clinical neuropsychological exam. With the assumption that integrity of the left hippocampus will reflect greater verbal learning and memory regardless of side of seizure focus, we analyzed all patients together for learning across repeated trials, immediate and delayed recall. Memory scores were correlated with left hippocampus BP (LH-BP) and left hippocampus volumes (LH-V).

Results: MTLE groups differed significantly in left and right hippocampal BP as well as in LH-V. Despite these differences, performance of the two patient groups improved similarly across learning trials. The total number of words learned, however, was significantly correlated with LH-V. Immediate recall after interference was correlated with LH-BP and LH-V. The correlation between delayed recall and LH-BP tended towards significance.

Conclusions: The present study reveals a link between verbal learning, retention and left hippocampal mGLUR5 availability, shedding light into molecular mechanisms underlying memory dysfunction in MTLE. These findings go beyond previous structural studies demonstrating a correlation between hippocampal size and memory deficits by providing mechanistic insights about the molecular underpinnings of cognitive function. mGLUR5 thus constitutes a potential biomarker for epileptogenesis and memory impairment in MTLE.

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LANGUAGE LATERALIZATION REPRESENTED BY SPATIOTEMPORAL MAPPING OF MAGNETOENCEPHALOGRAPHY

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Rationale: Evaluation of language lateralization is highly important for planning epilepsy surgery. Magnetoencephalography (MEG) is one of the potential tools for this purpose, however, conventional analysis by using a single dipole method may be sometimes erroneous. We assessed the usefulness of dynamic statistical parametric maps (dSPMs) for investigating language lateralization in patients with epilepsy.

Methods: MEG was performed for presurgical language mapping in ten epilepsy patients (male:3, female:7, age:9-34). Informed consent was obtained from each patient or guardian. All patients showed left language predominance in Wada test. MEG was recorded with a 306-channel whole-head system at a sampling rate of 600Hz. In all patients, high-resolution 3T anatomical MRI data were acquired with magnetization-prepared rapid acquisition gradient-echo (MPRAGE). For the paradigm of language testing, we performed a semantic language task. Patients were asked to decide whether each word was "abstract" or "concrete" in a visually presented series of words. The MEG data was averaged by using the timing of word presentation as a trigger. We calculated dSPMs by applying a distributed source model mapped on the MRI-derived cortical surface. The activation between 250ms and 550ms after the trigger was analyzed. In this study, we focused on the receptive language area (Wernicke's area), and included superior temporal, middle temporal, supramarginal and inferior parietal cortices on both hemispheres for further analysis. These areas were determined on the cortical surface reconstructed from each patient's MRI. Laterality index of dSPMs (LI-dSPMs) was obtained by LI = (L-R)/(L+R), where L and R is the number of unit dipoles with an F value higher than the threshold value in these cortical areas of left and right hemisphere, respectively. We also calculated equivalent current dipoles (ECDs) sequentially between 250ms and 550ms based on a single dipole model by using the left and right hemispheric sensors separately. Laterality index of ECDs (LI-ECDs) was obtained by LI = (L-R)/(L+R), where L and R is the number of ECDs with goodness of fit higher than 60%. (Foxe D, et al, AES annual meeting, 2003). For each patient, language predominance was determined based on the laterality index as follows; e"0.1:left, 0.1>LI>-0.1:bilateral, d"-0.1:right. We compared the results of LI-dSPMs and LI-ECDs with WADA test.

Results: All patients showed left language lateralization in LI-dSPMs. LI-dSPMs of the patients ranged from 0.10 to 0.37. In LI-ECDs, five patients showed left predominance, and five patients were bilateral. LI-ECDs ranged from -0.09 to 0.31. No patient showed right-sided language predominance in both LI-dSPMs and LI-ECDs.

Conclusions: In our patients, LI-dSPMs were more consistent with the language lateralization determined by WADA test than LI-ECDs. DSPMs may provide more reliable information in the analysis of language MEG data than a single dipole method.

3.210

EFFECT OF BRAIN-TO-SKULL CONDUCTIVITY RATIO ON EEG SOURCE LOCALIZATION FROM EPILEPTIFORM ACTIVITY

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Rationale: In majority of the EEG source localization methods, a piecewise homogenous head model is used to represent the physical properties of the human head volume conductor. This model usually consists of three compartments (brain, skull and scalp). The conductivities of different tissues are assigned to each compartment. It is usually assumed that the scalp has the same conductivity as the brain while the skull has a much lower conductivity. In addition, relative conductivities are considered to be important when source localization is concerned. Although many simulation studies had been carried out, to our knowledge, no previous experimental study concentrated on exploring the relationship between conductivity uncertainties and EEG source localization accuracy. In this study, we evaluated the influence of different brain-to-skull conductivity ratios (BSCRs) on EEG source localization from epileptiform activity.

Methods: High density EEG recordings utilizing a 76-electrode montage were obtained in a cohort of seven patients undergoing surgical evaluation for the treatment of medically intractable partial epilepsy. The patients were studied under a protocol approved by the Institutional Review Boards at the University of Minnesota and the Mayo Clinic (Rochester, MN). In order to evaluate the relationship between conductivity uncertainties and EEG source localization accuracy, we employed seven previously used BSCRs: 8, 15, 20, 25, 40, 80, and 120. For each BSCR, we performed the source reconstruction of interictal spike activities by using the LORETA algorithm. The accuracy of EEG source localization was assessed by comparing the estimated source activity to the resection area of brain which was regarded as the actual epileptiform source. The 8-18 interictal spikes were analyzed in this manner for each patient.

Results: In Patient 1, the post-operative MR images revealed a left frontal lobectomy. Eight interictal spikes were selected from the interical recordings. The source activity of LORETA analysis was localized to the epileptiform foci in the left frontal lobe of this patient. In addition, the source localization results by different BSCRs were similar to each other. The mean localization errors of all interictal spikes for different BSCRs for this patient ranged from 5.65 to 8.37 mm. The ANOVA statistical analysis indicated that there was no significant difference among seven BSCRs for the localization error ($p = 0.746$). In the remaining six patients, the same procedure of the source localization analysis was performed. The features of the source localization results by different BSCRs in these six patients were similar to those in Patient 1.

Conclusions: In this study, we have performed an experimental study in 7 epilepsy patients to investigate the relationship between conductivity uncertainties and EEG source localization accuracy. The present results suggest that the variability of the BSCRs does not significantly affect EEG source localization accuracy when comparing the estimated interictal epileptiform activity with the resection area or lesion of brain in epilepsy patients.

3.211

SOCIAL NETWORK THEORY APPLIED TO RESTING-STATE FMRI CONNECTIVITY DATA IN THE ANALYSIS OF EPILEPSY NETWORKS

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Rationale: Epilepsy networks tend to be persistently abnormal, and should therefore be defined by the extent and strength of their components in the interictal state. Based on this hypothesis, we used a combination of functional MRI connectivity data and social network analysis to determine if network properties could identify differences between controls and MTL patients. If so this would provide motivation for further assessment of network theory in this context. Resting-state fMRI connectivity studies may be helpful in localizing abnormal networks. For this work the network properties of various anatomically defined regions of interest in the interictal state were examined. The abnormal ROIs found either in individual patient or group level compared with normal controls could potentially provide insight into the understanding of the epilepsy networks and ultimately better identify targets for surgical intervention.

Methods: Applying social network theory methodology, we looked for abnormal network properties at the group level. A classifier algorithm

was tested to determine if resting-state network data allowed separation of medial temporal lobe epilepsy (MTLE) patients from normal control subjects. Five social network properties were applied to brain data including: Degree, Strength, Closeness, Clustering coefficient and Betweenness centrality, were selected for brain network analysis. FMRI Data of 52 control subjects and 16 patients who suffered from intractable MTLE were imaged on a 3T Siemens Trio scanner at the Yale MRRC. Resting state functional data was obtained using a gradient echo T2*-weighted EPI sequence with TR=1550ms, TE=30ms, flip angle=80, FOV=22 22cm, matrix size 64x64, 25 slices, functional voxel size 3.4mm 3.4mm 6mm. 3-8 runs of resting state data were collected with 229 volumes per run. 36 ROIs were defined in MNI space for analysis of network properties and this included a number of limbic regions. The five local network properties obtained from 36 anatomically defined volumes of interest (ROIs) were served as features to a classifier.

Results: Significant ($p<0.05$) abnormal network properties for a number of ROIs were identified in the patient group. A feature selection strategy was proposed to further improve the classification accuracy. An average sensitivity of 77.2% and specificity of 83.86% were achieved via 'leave one out' cross validation.

Conclusions: The finding of significantly abnormal ROIs in group level data confirms our initial hypothesis that network properties measured from resting-state fMRI data may reveal abnormal nodes involved in the epileptogenic network. Social network theory provides measures such as Degree, Strength, Closeness, Clustering coefficient and Betweenness centrality, that appear to serve as efficient features that can distinguish healthy volunteers from MTLE patients, even when these measures are based on data collected in the interictal state.

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CLUSTER ANALYSIS APPLIED TO FMRI DATA IN TYPICAL CHILDHOOD ABSENCE SEIZURES

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Rationale: Typical childhood absence seizures (CAS) are brief 5-10 second episodes, accompanied by short-term impairment of consciousness, and by 3Hz spike-and-wave discharges which begin and end abruptly on EEG. Recently, functional magnetic resonance imaging (fMRI) with simultaneous EEG recording has been instrumental for our current understanding of the anatomical and functional basis of CAS. These EEG-fMRI studies typically have used a general linear model (GLM) with a pre-defined hemodynamic response function (HRF) to assess dynamic changes of blood-oxygenation-level-dependent (BOLD) signal in whole brain, which reflects neuronal activation, albeit indirectly. However, there is some important evidence that the actual hemodynamic response for diverse brain regions may differ from the standard HRF.

Methods: We performed a model-free clustering approach to investigate BOLD changes during 51 CAS in 8 pediatric patients with typical childhood absence epilepsy (CAE). This approach has three steps, 1) the time courses of single voxels during the time period from -20s to +40 s relative to seizure onset were averaged across patients. 2) 116 gray matter anatomic volumes of interest (AVOI) were pre-defined from the SPM2 MRI template (MARSBAR), and the temporal correlations between pairs of mean time courses of AVOIs were computed. The number of expected clusters was determined by analyzing these correlations using a hierarchical clustering method. 3) Correlations between each pair of time courses of voxels were computed. Then we performed a k-mean method to create partitions of voxels exhibiting similar time courses, using the number of expected clusters obtained from step 2.

Results: We found that 116 AVOIs can be divided into four clusters by using the hierarchical clustering method. By applying the k-mean method, the partition of areas into clusters emerged as follows: 1) thalamus and occipital cortex; 2) lateral and part of medial parietal cortex, medial temporal, basal ganglia, and cerebellum; 3) part of medial frontal, lateral frontal, orbital frontal, and rolandic cortices; 4) part of medial frontal, medial parietal, medial temporal cortices and insula. Furthermore, we observed that fMRI change of the cluster involving thalamus and occipital cortex was closer to the conventional HRF, and changes of the other three clusters appeared to differ greatly from the conventional HRF.

Conclusions: Our results demonstrate a complex sequence of fMRI changes in absence seizures, which are not detectible using conventional HRF modeling. These results also revealed that current clustering methods can effectively identify regions of similar activation. Finally, our present findings suggest that the clustering method might be a very useful tool for analysis of activation patterns in fMRI for other types of generalized seizures.

3.213

LOCALIZATION OF EPILEPTIC AND FUNCTIONAL NETWORKS AT REST USING INDEPENDENT COMPONENT AND FUNCTIONAL CONNECTIVITY ANALYSIS OF THE BOLD SIGNAL

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Rationale: Recent fMRI studies suggest that networks participating in cognitive funtion show correlated fluctuations of the BOLD signal at rest. Some patients with focal epilepsy show stereotyped onset zones and spreading network of seizure activity. We investigated if these pathological networks show correlated activity and a specific connectivity pattern in resting state fMRI recordings in patients undergoing epilepsy surgery for medically-intractable partial epilepsy. To test the feasibility of our methods to detect brain areas showing correlated BOLD fluctuations, we also computed connectivity maps for functional networks such as language. Functional and pathological networks were also defined using implanted subdural electrodes by recording ictal onset and spread patters as well as electrical stimulation mapping (ESM).

Methods: Resting state fMRI was recorded on a 3T GE scanner in four patients with medically intractable focal epilepsy prior to implantation of subdural electrodes. Electrodes were localized using post-implantation CT and MRI followed by alignment to the surface of the pre-implantation MRI. BOLD signal was subjected to independent component analysis (ICA) as implemented in FSL (MELODIC) and functional connectivity analysis (RSFC). As seeds for RSFC we used

region of interests below electrodes showing either epileptic activity and in two patients below electrodes that showed language function as defined with electrical stimulation mapping.

Results: ICA components overlapping with subregions of the ictal onset zone were demonstrated in three patients. (an example is shown in figure 1). Similarly, only parts of the functional connectivity maps overlapped with epileptic networks defined with the subdural electrodes. The functional networks showed a trend to increased local connectivity and decreased connectivity with the contra-lateral hemisphere in two patients. RSFA reliably detected language areas showing the feasibility of our approach to detect functional resting networks.

Conclusions: Parts of epileptic networks show correlated BOLD activity at rest. However, ICA and RSFC as used here showed little sensitivity to map the epileptic areas as defined with subdural electrodes. A combined approach, possibly including other methods such as single pulse cortically evoked potentials, that was recorded in these patients as well, might prove to increase the sensitivity.

RSFC successfully localized anatomically and ESM defined language areas.

IMAGE: images/908234_A.jpg

Fig. 1: Overlay of a resting state ICA component (yellow) and electrodes that showed seizure activity (blue) in one patient.

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EEG-FMRI BOLD RESPONSE ASSOCIATED WITH DIFFUSE BILATERAL EEG EVENTS IN FOCAL EPILEPSY PATIENTS

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Rationale: Patients with partial epilepsy may show diffuse bilateral EEG discharges believed to be propagation from their focus. In some, this is the only scalp EEG manifestation, making it difficult to distinguish it from a generalized seizure disorder. Previous studies described the EEG-fMRI characteristics of generalized spike and wave discharges (GSWD) in idiopathic generalized epilepsy (IGE). Here we describe the EEG-fMRI response to diffuse bilateral discharges in focal epilepsy patients.

Methods: Fourteen patients with focal epilepsy and diffuse bilateral discharges underwent an EEG-fMRI study. Some had focal interictal discharges as well, which were analyzed separately. EEG discharges were marked and convolved with four hemodynamic response functions (peaks at 3-9s). Significant responses were defined with $|t|>3.1$ and spatial extent of 4 voxels ($p=0.05$, corrected). Visual analysis and comparison with EEG and clinical data was performed.

Results: Five patients had diffuse bilateral EEG events without side predominance: four showed lateralized EEG-fMRI results. The fifth had symmetric fMRI activation and deactivation that did not match the known EEG-fMRI pattern of IGE. Nine patients had lateralized EEG predominance: seven of them had matching EEG-fMRI activation asymmetry, and two others had matching deactivation asymmetry (matching was defined as higher $|t|$ in the corresponding side or region of EEG maximum). All 14 patients had some to most of the components of the default mode network in deactivation maps: precuneus, posterior cingulate gyrus, medial prefrontal lobe, and parts of associative parietal cortices bilaterally. However, this pattern was not complete and showed asymmetry in eight patients. Activation patterns varied among patients, although activation of frontal, insular, and perisylvian regions, similar to responses to GSWD, was frequently seen. A thalamic response was less reliable than what was reported in IGE: five patients had no response, six showed activation stronger in anterior thalamus, two had a deactivation in posterior thalamus, and one showed both thalamic activation and deactivation. Caudate response was uncommon: only two patients showed a caudate deactivation -a common finding in IGE.

Conclusions: Our results show EEG-fMRI result differences between diffuse bilateral discharges and the known patterns of IGE. Cortical activation seems the most reliable finding, showing lateralization or focal accentuation. Cortical deactivation was less lateralized and consistently overlapping parts of the default mode network. Thalami showed activation, deactivation, or both in some of the patients. An ipsilateral stronger thalamic response was the most likely. These findings may be due to a stronger BOLD response in the primary focus of the discharges, followed by a weaker response related to propagation. In conclusion, EEG-fMRI can be considered as a method to distinguish diffuse bilateral discharges in focal epilepsy from a genuine generalized process, especially in the absence of a more localizing feature.

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LOCALIZING SEIZURE ONSET ZONE USING ICTAL SPECT AT VARYING THRESHOLDS

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Rationale: Medically refractory epilepsy is often amenable to surgery. One technique used to identify the epileptogenic zone is the subtraction ictal SPECT coregistered to MRI (SISCOM). However, SISCOM does have several limitations. One limitation is the threshold to use when comparing areas of ictal hyperperfusion compared to the interictal SPECT study. Traditionally, a z score of 2 is used as the threshold. Some may vary the threshold for each individual, but no study has been performed to systematically examine the specificity and sensitivity of different z scores. Furthermore, several perfusion patterns may emerge at each threshold. These patterns may reflect both the seizure onset and propagation which may provide important localizing information. Most previous studies did not take into account the observed patterns of hyperperfusion and only take the most hyperperfused region to represent the seizure onset zone. In this study we investigated the location and patterns of hyperperfused regions using different z thresholds. We propose that for each patient the z threshold should be based on the observed patterns of hyperperfusion to achieve the most accurate result.

Methods: A database of over 300 patients who underwent surgical resection for refractory epilepsy was reviewed. The surgical sites were both temporal and extratemporal. Approximately 70 patients who had an ictal and interictal SPECT and both a pre- and post-operative MRI were identified. From these patients 28 (mean age 33 years old, range 2-65) have remained seizure free for at least 6 months. Post-surgical MRI was co-registered with pre-MRI using MINPAV and SPM (Matlab). SISCOM was performed to both pre- and post-operative MRI. The location and patterns of hyperperfused regions at varying z thresholds were compared using MRIcro. The epileptogenic zone was defined as the site of surgical resection and seizure freedom.

Results: We found that the optimal threshold for SPECT-SISCOM localization of the epileptogenic zone was between 1.5 to 2 standard

deviations (1.5 SD n= 15, 54%; 2.0 SD n= 12, 43%). Notably, in patients who were either not localized or incorrectly localized according to our standard SPECT-SISCOM localization criteria (n=12), we identified a focus of hyperperfusion that co-localized with the site of resection in 7 patients (58%) when SPECT-SISCOM was thresholded at 1.5 standard deviation. Figure 1 shows representative SPECT images of one patient at varying z thresholds overlaid on the postoperative MRI. The threshold of 1.5 showed optimal sensitivity, with an hour-glass pattern of hyperperfusion overlapped with the resected area.

Conclusions: SISCOM is a useful modality in evaluation of patients for epilepsy surgery. Although a z score of 2 is traditionally used, this threshold may not be optimal for every patient. Our preliminary studies suggest a z score of 1.5 may increase the sensitivity in some patients. We propose that the determination of z score threshold should be guided by the observed patterns of hyperperfusion, which reflect different degrees of seizure propagation.

IMAGE: images/906819_A.jpg

Figure 1. Representative subtraction ictal SPECT images of one patient at thresholds of 1, 1.5, 2, and 2.5 standard deviations (SD) overlaid on the patient's postoperative MRI.

3.216

3.0T-FUNCTIONAL MRI CAN DETECT DOMINANT HEMISPHERE CONTRIBUTING MEMORY FUNCTION IN THE PATIENT WITH MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Temporal lobe resection benefts many patients with refractory temporal lobe epilepsy, however may be complicated by memory impairments typically of verbal memory following temporal lobe resection. The Wada test is widely used procedure to detect deminant hemispere as well as predict postoperative memory deficits, however, has a number of disadvantages, notably the fact that it is an expensive and invasive procedure. Functional MRI(fMRI) has potential for replacing Wada test and providing additional memory function data. We examined whether Wada test can be replaced by fMRI to detect dominant hemisphere.

Methods: Using 3.0T-functional MRI(fMRI), we tried to preoperatively detect dmominant hemisphere in the patient with mesial temporal lobe epilepsy(MTLE). Five patients(median age48.6; range 20-51 years; one left-handed) with mesial TLE(three had left MTLE) underwent fMRI session each consisting of 16 words. Patients were instructed to memorize the words coming from headphone during scanning. Just after each session, patients were given memory test for the words recieved in the scanner and to attempt to recall as many of the words as possible. All data were analyzed using Statistical Parametric Mapping software(SPM2). These data obtained from fMRI was compared with the result of Wada test.

Results: Two of five patients showed left mesial temporal lobe activation, two patients showed bilateral mesial temporal lobe activation, and one patient showed right side activation. On the other hand, Wada test revealed left hemisphere dominance in all but one patient. This patient was left-handed and confirmed to be right hemisphere dominant for language on both fMRI and the Wada test.

Conclusions: The fMRI may be an useful non-invasive test for detecting dominant hemisphere contributing memory function. Language fMRI might reduce the necessity of the Wada test for language lateralization, especially in TLE.

3.217

CORRELATION OF PRE-SURGICAL PET, MRI AND INTRACRANIAL EEG WITH PATHOLOGIC FINDINGS IN PEDIATRIC EPILEPSY SURGERY

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Rationale: The degree of success of epilepsy surgery is influenced by the ability to localize the epileptogenic focus.

Imaging studies such as MRI and 18[F]fluorodeoxyglucose Positron Emission Tomography (FDG-PET) have been used to identify or confirm ictal foci in preparation for surgery. To our knowledge, there is little information about the correlation between PET, MRI, intracranial EEG (icEEG), and pathological findings in the pediatric population. The main goal of this study is to compare these four modalities. Our second goal is to examine the hypothesis that PET scans are more sensitive than MRI in localizing epileptogenic areas.

Methods: We reviewed medical records of thirty-eight patients, ages 1 to 17 years, with medically refractory epilepsy who underwent removal of the epileptogenic focus at the University of Chicago between May 2006 and March 2010. Patients with pre-operative MRI and PET, and post-operative pathology on file were included in the study (n=20). In all patients, epileptogenic foci were identified pre-operatively by icEEG monitoring. After removal, surgical specimens were analyzed by inspection of their gross anatomy, as well as by standard staining for cytological architecture, and immunohystochemistry. Pathological findings were then compared to the findings on pre-operative icEEG, MRI and PET.

Results: Intracranial EEG was used as the gold standard method for localization of the epileptogenic foci. All the patients in our series (n=20) had focal icEEG findings. PET scans showed abnormal findings in 75% (n=15) of cases. One PET positive patient showed bilateral focal hypometabolism. 13 patients with lateralizing PET demonstrated regional cortical hypometabolism ipsilateral to the icEEG focus. One showed an ipsilateral hypermetabolic focus. PET provided correct lobar localization in 64% (n=9) of these patients. MRI was abnormal in 55% (n=11) of cases. Of these patients, one had a non-lateralizing abnormality (partial agenesis of the corpus callosum), and the other had a lesion contralateral to the epileptogenic focus. The rest 45% (n=9) patients had ipsilateral MRI abnormalities. All nine patients who had lesions on MRI also had abnormal findings on PET scan. Pathological examination of the ictal foci identified by icEEG revealed abnormal findings in 70% (n=14) of cases in our series. Of the patients with abnormal PET (n=15), 80% (n=12) had abnormal pathological findings.

Conclusions: This study highlights the importance of including PET scans in the pre-operative workup for epilepsy surgery in the pediatric population. Our results suggest the following: 1. PET is more sensitive than MRI in identifying abnormal areas in the brain. 2. Although PET accurately lateralized the side of abnormal function, it was able to precisely localize epileptogenic foci in 64% of cases; therefore, icEEG monitoring must be used to further define these areas. 3. 80% of cases

with abnormal PET demonstrated abnormal pathological findings these areas.

3.218

USEFULNESS OF SPM ANALYSIS OF FDG PET IN DETECTING EPILEPTOGENIC TUBER AND CORTEX IN TUBEROUS SCLEROSIS COMPLEX

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Rationale: To evaluate the diagnostic value of statistical parametric mapping (SPM) analysis of FDG PET in localizing epileptogenic tuber/cortex in tuberous sclerosis complex (TSC).

Methods: Nineteen patients with intractable epilepsy from TSC had comprehensive presurgical evaluation including FDG PET and intracranial EEG, and underwent resective surgery. The single most hypometabolic region determined by SPM analysis of FDG PET was compared with epileptogenic zone on intracranial EEG, as well as postoperative surgical outcome. For SPM analysis, the cutoff threshold was adjusted to detect the single most hypometabolic region.

Results: SPM analysis of FDG PET visualized single most hypometabolic region which was concordant with intracranial EEG in 53% (10/19) while visual analysis failed to localize in all 19 patients. SPM analysis tended to be more accurate in localizing epileptogenic tuber/cortex in the patients aged above 6 years (71%, 5/7 vs. 42%, 5/12 in the patients younger than 6 years). Postoperative seizure-free outcome was likely to be higher in the patients with localizing epileptogenic tuber/cortex on SPM analysis (70%, 7/10 vs. 44%, 4/9 in the patients without localizing epileptogenic tuber/cortex)

Conclusions: Our data suggest SPM analysis of FDG PET is a useful non-invasive method for localizing epileptogenic tuber/cortex, and it is more helpful in older children with TSC.

3.219

EFFECT OF TEMPORAL LOBE EPILEPSY ON THE DEFAULT MODE NETWORK

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Rationale: The default mode network (DMN) of the brain is involved in consciousness and is disrupted in several neurologic diseases. Epilepsy is associated with cognitive deficits and the effects of epilepsy on the DMN have not been elucidated. We evaluated the DMN in temporal lobe epilepsy (TLE) using resting state functional MRI (fMRI) connectivity analysis, a technique that analyzes hemodynamic coherence of a 'seed area' and non-invasively maps the underlying associated network.

Methods: Seeds 6 mm in diameter were defined in the retrosplenium/precuneus region in 5 subjects with right TLE (R-TLE), 5 with left TLE (L-TLE), and 6 control subjects during the resting state. The DMN associated with this seed was compared between the groups using whole-brain independent t-tests conducted for each group pair (cluster corrected, $z > 2.0$, $p < 0.05$). Analyses were done using the FEAT component of FSL (FMRIB's software library, Oxford University, UK).

Results: A DMN was demonstrable in all 3 subject groups. Compared to control subjects, the DMN observed in L-TLE was significantly larger than controls and the DMN observed in R-TLE was significantly smaller. Other comparisons did not yield significant results (see table and images).

Conclusions: The DMN observed by coherence to the retrosplenium/precuneus was found to be smaller in R-TLE and larger in L-TLE. The effect of TLE on the DMN is expected considering that the retrosplenium is heavily interconnected with the medial temporal lobe, which provides 40% of its extrinsic input (1). Involvement of the DMN may be relevant to the cognitive change differences between R-TLE and L-TLE and is possibly part of the mechanism of cognitive impairment during seizures for R-TLE and L-TLE.

Ref: 1. Kobayashi & Amaral 2003

IMAGE: tables/904327_T1.jpg

IMAGE: images/904327_A.jpg

3.220

FDG-PET AND SPECT CO-REGISTRATION FOR DETECTION OF EPILEPTOGENIC ZONE IN PATIENTS WITH NON-LESIONAL NEOCORTICAL EPILEPSY

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Rationale: In intractable neocortical epilepsy patients with normal magnetic resonance imaging (MRI), subtraction ictal single photon emission computed tomography (SPECT) co-registered to MRI or fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET)/MRI co-registration are techniques that were recently reported to improve detection of the epileptogenic region. By combining these methods, we hypothesize that subtraction ictal SPECT, FDG-PET and MRI image co-registration provides additional localizing information enhancing the detection of epileptogenic focus.

Methods: We identified all patients with normal MRI who had interictal FDG-PET, an ictal and interictal SPECT during their presurgical evaluation between 2004 to 2009 and had undergone resective surgery and followed up for at least 6 months. Magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) MRI, FDG-PET and SPECT images were co-registered using automated registration algorithm based on mutual information within SPM2. SPECT ictal-interictal difference image was created by subtracting the interictal SPECT image from the ictal image. This was then simultaneously displayed with FDG-PET and MPRAGE MRI sequence to identify congruent areas of hyperperfusion and hypometabolism . The area of resection and the region of MRI-PET-SPECT congruency were compared and the results were validated through seizure outcome analyses.

Results: Twenty neocortical epilepsy patients (female n = 9; median 21 years; IQR: 9.3-29.5) were studied. All patients underwent invasive electroencephalography evaluation prior to surgical resection. Subtraction ictal SPECT, FDG-PET and MPRAGE MRI image co-registration allowed anatomic localization of concordant/discordant FDG-PET and SPECT abnormalities. Co-localized FDG-PET and SPECT abnormality was identified in 13 (65%) patients. Resection of the cortical area corresponding to the co-localized abnormality was strongly associated with a seizure-free outcome (p=0.017).

Conclusions: The co-localization of PET/ictal SPECT abnormalities may enhance accurate detection of the epileptogenic region in the challenging group of patients with medically intractable neocortical epilepsy and normal MRI.

3.221

IDENTIFICATION OF EPILEPTIFORM ACTIVITY USING ECONNECTOME

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Rationale: There has been a growing interest in using interictal spikes as markers of the epileptiform activity. It has been shown in some studies that regions where interictal spikes originate are correlated to the epileptogenic areas. Previously in our lab, a causality measure was developed to study the connectivity among multiple interictal spike origins and identify the primary epileptic source. In this study, we investigate the concept of combining cortical source imaging and causality estimation to localize epilepsy sources in patients with intractable epilepsy.

Methods: 76-channel Electroencephalography (EEG) signals prior to operations were recorded from 7 epilepsy patients, who were not responsive to medications and had to undergo surgical resections. These patients had significant reduction in seizures or became entirely seizure free after operation. Computational analysis was carried out using eConnectome (econnectome.umn.edu), an open-source software developed at the University of Minnesota. 10 interictal spikes from each patient were selected and averaged to improve the signal to noise ratio. The averaged waveforms were then fed into the eConnectome software to estimate cortical current density (CCD) distributions for the duration of a spike. If multiple regions of interest (ROI) were present, a causal analysis, namely directed transfer function (DTF), was applied to identify the primary cortical source. The results were compared to post-operative magnetic resonance imaging (MRI) data and clinical reports which indicate foci identified by the epileptologists.

Results: In 6 out of 7 patients, the identified primary source locations are in accord with clinically-defined seizure onset zones. In 1 patient the identified source is localized within the same frontal lobe. Among the 6 patients where satisfactory results were achieved, 4 showed multiple active sites during interictal spikes. The primary sources that have the most information outflow are consistent with the epileptogenic foci identified by the epileptologists.

Conclusions: Noninvasive EEG source imaging and connectivity analysis were employed to study cortical generators of interictal spikes. Using eConnectome software, the identified cortical foci of interictal spike activity are overlapping or in close proximity with surgical resection sites. These encouraging results suggest the feasibility of using of interictal spikes in localizing epileptic sources. Further investigation is needed when individual subject's MRI data are used to quantify the estimation error.

3.222

NON-INVASIVELY RECONSTRUCTING EPILEPTOGENIC ZONES USING SCALP MEG DATA FOR PRE-SURGICAL EVALUATION

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Rationale: The goal of the present study is to use a novel computational source reconstruction algorithm, i.e., variation-based sparse cortical current density (VB-SCCD) method, to noninvasively reconstruct epileptogenic zones from the external magnetoencephalography (MEG) in patients with intractable epilepsy. The availability of the non-invasive technology is paramount valuable for the pre-surgical planning in epilepsy, as compared with the current invasive procedure in clinics.

Methods: Three patients with medically refractory epilepsy were studied. Each of patients received an MRI scan of the head. High density MEG was spontaneously recorded for 10-20 minutes with 148-channel whole-head magnetometer (Magnes WH2500, 4-D Neuroimaging, San Diego, CA, USA) in a magnetically shield room. 24, 58, 30 interictal spikes were selected, marked and analyzed respectively for three patients, and results were confirmed by experienced neurologists. The performance was evaluated by comparing with non-invasively imaged epileptogenic zones and those identified by lesional MRI, as well as presurgical evaluation outcomes.

Results: Our results suggest that the reconstructed cortical sources behind interictal spikes using VB-SCCD are consistent with presurgical diagnosis of cortical tubers and outcomes of resection in terms of location in all three patients and in all studied interictal spikes (figure 1). The spatial distributions of cortical sources in each patient are consistent across multiple different interictal spikes.

Conclusions: The present study shows the promising capability of the novel VB-SCCD method in non-invasively estimating locations of epileptogenic zones underlying interictal spikes with external magnetic signal.

IMAGE: images/905600_A.jpg

3.223

THE CLINICAL VALUE OF MAGNETOENCEPHALOGRAPHY IN EPILEPTIC CHILDREN WITH FRONTAL LOBE TUMORS: TWO CASES

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Rationale: To demonstrate how magnetoencephalography (MEG) provides helpful epileptic-focus and functional brain mapping for the presurgical evaluation of patients with frontal tumors and epilepsy, which may obviate the need for invasive Phase II intracranial electrode evaluation.

Methods: We report two pediatric cases with frontal tumor-related epilepsy. In case 1, a 16-year-old girl with a nonenhancing left frontal tumor (previously biopsied, with provisional diagnosis dysembryoplastic neuroepithelial tumor (DNET)), electroencephalography (EEG) showed rare focal sharp waves in the left central region during sleep. In case 2, a 12-year-old boy with a well-circumscribed, nonenhancing left frontal cortical tumor, EEG findings showed intermittent focal slowing in the left frontal region. Spontaneous MEG data were collected with a 306-channel Elekta-Neuromag whole-head MEG system, and equivalent current dipoles (ECDs) of interictal spikes were localized. Also, median-nerve somatosensory and auditory evoked responses were localized, and dichotic language hemispheric dominance was determined, using MEG. The spontaneous and evoked ECDs were superimposed on patients' brain MRI scans.

Results: MEG analysis showed that all interictal spikes were localized to the anterior border of the left frontal tumor in Case 1; and to the posterior-inferior tumor border in Case 2; both with intermittent associated focal left-frontal slowing. Comparing the MEG and EEG results: in case 1, unlike MEG, the EEG could not localize the epileptiform spike activity within the left frontal lobe; and the intraoperative ECoG results were negative for spikes. In case 2, unlike MEG, the EEG did not adequately localize the spikes to the left frontal tumor area. In both cases, MEG showed auditory and somatosensory cortices to be more than one gyrus distant from the tumor; both patients had left-hemisphere language dominance. For both patients, neurosurgery with complete tumor resection was performed after reviewing the MEG results, bypassing phase II EEG. Patient 1 had a final pathologic diagnosis of ganglioglioma WHO Grade 2; and Patient 2 had diagnosis of DNET. The surgical outcomes were good for these two cases, without functional deficits. The patients were seizure-free at postoperative 3 and 6 months, respectively.

Conclusions: These case studies show that MEG is a powerful and accurate noninvasive technique which can provide useful information regarding epileptic foci and functional brain mapping for presurgical planning of epilepsy patients with frontal tumors. MEG may be used to bypass invasive phase II EEG for presurgical evaluation of epilepsy patients with frontal brain tumors.

Patient clinical records & findings

IMAGE: tables/907271_T1.jpg

IMAGE: images/907271_A.jpg

3.224

FMRI LANGUAGE DOMINANCE AND FDG-PET HYPOMETABOLISM

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Rationale: Atypical language dominance is common in patients with temporal lobe epilepsy. We examined the association of left temporal hypometabolism with laterality of fMRI activation in a language task.

Methods: 30 patients with temporal lobe epilepsy [mean age 32.4±11.0 years (range 18-55); epilepsy onset 15.3±11.3 years (range 0.8-40); 22 left focus, 8 right focus], had FDG-PET using non-invasive cardiac input function. After MRI-based partial volume correction, regional glucose metabolism (CMRglc) was measured and asymmetry index, AI=2(L-R)/(L+R), calculated. fMRI language dominance was assessed with an auditory definition decision paradigm at 3T. fMRI data were analyzed in SPM2 using ROIs from Wake Forest PickAtlas [Wernicke's Area (WA), Inferior Frontal Gyrus (IFG), Middle Frontal Gyrus (MFG)] and bootstrap Laterality Index, LI=(L-R/L+R).

Results: 19 patients had ipsilateral temporal hypometabolism; 3 of 4 patients with atypical language had abnormal FDG-PET. Increasing left mid-temporal hypometabolism correlated with decreased MFG LI ($r=-0.41$, $p<0.05$) and showed trends with WA LI ($r=-0.37$, $p=0.055$) and IFG LI ($r= -0.31$, $p=0.099$); these relationships became more significant after controlling for age of onset. Increasing hypometabolism was associated with fewer activated voxels in WA ipsilateral to the focus and more activated voxels contralaterally, but overall, activation amount in left WA was similar to subjects without left temporal hypometabolism ($t=-1.39$, $p>0.10$).

Conclusions: We did not find evidence of impaired BOLD response in hypometabolic cortex. Decreased laterality in the presence of increased hypometabolism likely reflects disrupted left temporal lobe function. Regional hypometabolism may explain why some patients with MTS and normal MRI show atypical language.

3.225

INTERICTAL MRI PERFUSION ABNORMALITIES OBSERVED BY ARTERIAL SPIN LABELLED SEQUENCES IN FOCAL EPILEPSIES

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Rationale: We aimed to describe the interictal perfusion patterns seen in focal epilepsies by Arterial Spin Labelled sequences, as well as to evaluate its possible localization value.

Methods: This is a cross-sectional study of 50 consecutive focal epilepsies diagnosed by semiology, structural MRI and EEG, who underwent a 3 TESLA MRI epilepsy protocol that included ASL sequences. Images were reviewed by two neuroradiologists. Perfusion abnormalities were classified as focal, or hemispheric when compared side by side.

Results: The sample had 50% female, medium age 42.9 (±17.2) years-old. Fifty-eight percent were symptomatic epilepsies and 73% refractory to treatment. The most frequent etiology was Malformation of Cortical Development (18%), followed by strokes (165) and tumors (12%). Lobe classification showed 48% of temporal, 30% frontal and 22% of posterior neocortical epilepsies. Complex partial seizures were the most frequent type (48%).

Visual analyses of ASL sequences showed 80% evidences of perfusion interhemispheric asymmetries. Such abnormalities were more likely to be observed in patients with left hemispheric epileptogenic focus ($p<0.05$). There was a statistical tendency to observed hyperperfusion over the epileptogenic hemisphere. Up to 25% of patients had focal perfusion tighly correlated to the epileptogenic area as seen by EEG, enhanced focal perfusion was more likely to be observed.

Conclusions: Interictal perfusion abnormalities analyzed by ASL sequences are very often observed in patients with focal epilepsies.

Hyperperfusion is more likely to be observed over the epileptogenic area, and the ipsilateral hemisphere as well.

3.226

ICTAL-MRI FOCAL HYPERPERFUSION LOCALIZES THE EPILEPTOGENIC ZONE USING ARTERIAL SPIN LABELED SEQUENCES

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Rationale: We aim to describe the Ictal perfusion abnormalities seen by arterial spin labeled sequences (ASL) of MRI in single partial seizures.

Methods: We report two cases of patients with focal epilepsies that underwent an ictal-MRI that included ASL, during a single parcial seizure. Case 1 was a right temporal posttraumatic epilepsy, experiencing complex partial seizures characterized by ictal verbalization. Structural MRI showed right temporal microbleedings suggestive of posttraumatic axonal injury. Case 2 was a right posterotemporal tumoral epilepsy, having audiogenic seizures. Structural MRI showed a tumor located in the right middle temporal gyrus.

Results: Both cases showed an area of hyperperfusion seen by ASL matching the area of seizure onset as recorded in a prior Video-EEG monitoring. Such findings were normalized in a follow-up MRI one month later, with patients seizure free for more than 24 hours. In Case 1 language dominance was located with functional-MRI (BOLD) over the left hemisphere. In case 2 findings on ASL were exactly correlated to the images obtained by SISCOM.

Conclusions: Focal hyperperfusion observed by Ictal-MRI in single focal seizures, may have localizing value; since they are well correlated to clinical, EEG and SPECT findings.

3.227

THE USEFULNESS OF DOUBLE DENSITY OPTICAL TOPOGRAPHY

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Rationale: Optical topography (=OT) is a noninvasive method for measuring regional cerebral blood volume (rCBV) change using near-infrared light. In conventional OT, the 30mm distance between light source and detector make it possible for the emitted light to reach the cerebral cortex, at a depth of approximately 20mm from the scalp. The maximum disadvantage of conventional OT is the low spatial resolution. To improve this shortage, we developed the double spatial density OT. In this study we will show two advantages of DD-OT. One is twice spatial resolution and the other is more stable measurement than the conventional OT.

Methods: We developed the double spatial density OT by putting another pair of transmitting-sensor probe between original pair of probes, which make us possible to measure the rCBV by 1.5cm interval. Using the double density OT (DD-OT), we compared the spatial distribution of HbOxy change during motor, sensory and language stimulation with single density OT in 5 normal volunteers. With 3D-magnetic sensor, we superimposed the changes of rCBV onto the MRI surface images and evaluated the spatial resolution of both type of OT on it. To reveal the usefulness of DDOT for detecting epileptic focus, we performed rCBV by DD-OT on neocortical epileptic patients. Increasing area of rCBV measured by ictal DD-OT during phase1 monitoring were compared with epileptic focus detected by grid electrodes inserted on cortical surface in phase 2 monitoring.

Results: The peak of rCBV changes by finger tapping and sensory task were showed on the motor cortex and sensory cortex, respectively, on the MRI surface image. The valley line of these two peaks of rCBV is identical to the central sulcus detected by MRI image. The results of ictal DD-OT of intractable neocortical epilepsy patient are also identical to the results of ictal EEG recording with the subdural grid electrodes.

Conclusions: DD-OT showed more precise, fine and stable distribution of rCBV changes on MRI images during the task. DD-OT showed higher spatial resolution comparing with conventional OT and is useful for precise functional brain mapping or epileptic foci diagnosis.

3.228

THALAMIC HYPERPERFUSION USING PULSE ARTERIAL SPIN LABELING IN GENERALIZED EPILEPSY

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Rationale: The pathophysiology of generalized spike and wave is unclear with reticular, thalamic and cortical origins proposed. fMRI has been used most commonly to study hemodynamic changes during absence seizures. ASL has also shown activation in candidate regions but surprisingly only rare observations of thalamic involvemnent in some series. We observed PASL changes on routine MRI in a subject with generalized epilepsy.

Methods: 29-year-old female with onset of absence seizures and tonic-clonic seizures in childhood which were controlled with Valproate. Multiple EEGs over years had shown generalized 3 hertz spike and wave. Due to concerns of teratogenicity, anticonvulsant medication was switched to levetiracetam at patients request. Breakthrough seizures occurred every few months due to either medication failure or stress of work and sleep deprivation. MRI was done because of report of intermittent focal neurological symptoms.

Results: EEG revealed 3 Hz spike and wave discharges with prominent activation by hyperventilation. Routine MRI sequences did not demonstrate any focal abnormalities. PASL images were found to show a discrete area of hyperperfusion in the medial, bilateral thalami. Simultaneous EEG was not obtained at the time of MRI acquisition.

Conclusions: Demonstration of thalamic activation using ASL sequences has not been perforemd as frequently as fMRI. The failure to identify this response in some cases may be due to a number of reasons including spike frequency, MRI magnet strength and subtle electroclinical differences. Our case shows thalamic PASL activation in a case of primary generalized epilepsy which has only reported on rare

occasions in secondary generalised epilepsy to our knowledge. More studies with larger numbers of patients are needed to clarify these findings.

IMAGE: images/905933_A.jpg

3.229

SINGLE-TRIAL CORTICAL MAPPING OF SENSORIMOTOR ORGANIZATION IN REAL-TIME

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Rationale: Functional mapping of eloquent cortex is often a necessary component of brain surgery planning, but current stimulation techniques are inefficient and can provoke unwanted seizures. Here, we present a new rapid, accurate, and practical mapping system that extracts relevant event-related cortical activity from passive electrocorticographic (ECoG) recordings while patients carry out simple behavior. Unlike previous related methodologies, this novel mapping procedure is designed to demonstrate single-trial event-related spectral alterations to localize and discriminate sensory and motor cortices.

Methods: We evaluated 10 patients with epilepsy on a series of motor tasks including simple speech articulation and hand button press. Events were detected precisely with a standard analog output microphone and button press box. ECoG signal was recorded and processed in real-time (with updating every 50 ms) along with event detection. We created a user-friendly interface that displays 1) continuous spectral power, 2) single-trial event-related spectrogram, and 3) running average of event-related spectrograms.

Results: For speech sounds, we could rapidly localize the motor cortex corresponding to lip and tongue articulators, as well as, sensory feedback in the lateral auditory cortex. For button press, we could easily localize the hand motor and sensory cortex. Motor function was distinguished from sensory function by evaluation of the temporal relationship of cortical activation to event onset. Finally, our passive mapping results demonstrated high concordance with results derived using blinded electrical cortical stimulation mapping. The results show that our procedure derives a complete functional motor and sensory cortical map in seconds, and usually less than 15 trials.

Conclusions: In summary, we demonstrate a novel and practical cortical mapping procedure as a new tool for neuroscientific and clinical application.

IMAGE: images/907717_A.jpg

Single-trial (stacked) on an 8x8 subdural grid, while a patient was saying “Ba”. Dotted line in each electrode graph shows speech onset. Cortical activation before onset (left of dotted line) correspondence to speech motor cortex in the ventral precentral gyrus. Activations after onset (right of dotted line) are located in the auditory cortex in the posterior superior temporal gyrus.

3.230

INCREASED IN VIVO EXPRESSION OF AN INFLAMMATORY MARKER IN TEMPORAL LOBE EPILEPSY

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Rationale: Animal studies and clinical observations suggest that epilepsy is associated with inflammation. Translocator protein 18 kDa (TSPO) is a marker of inflammation and can be measured in the living human brain with positron emission tomography (PET) and the radioligand 11C-PBR28. In this study, we sought to determine if TSPO expression is increased ipsilateral to the seizure focus in patients with temporal lobe epilepsy.

Methods: Ten patients with unilateral temporal lobe epilepsy and seven healthy subjects were studied with 11C-PBR28 PET and magnetic resonance imaging (MRI). Uptake of radioactivity after injection of 11C-PBR28 was measured from regions of interest drawn bilaterally onto MR images. Brain uptake from ipsilateral and contralateral hemispheres was compared using a paired samples t-test.

Results: Brain uptake was 10% higher ipsilateral to the seizure focus in the hippocampus, but not in other brain regions. This asymmetry was more pronounced in patients with hippocampal sclerosis than in those without. Both in healthy subjects and in patients with epilepsy, we noted small foci of higher uptake within the hippocampi; in these foci, uptake was 22% higher ipsilateral to the seizure focus in the patients. In healthy subjects, no hemispheric asymmetry in brain uptake was seen either in whole hippocampus or in foci of higher uptake.

Conclusions: We found evidence for increased expression of TSPO in ipsilateral hippocampus of patients with temporal lobe epilepsy. Our results suggest that inflammatory processes may play a role in the pathophysiology of temporal lobe epilepsy.

3.231

HEMODYNAMIC CHANGES DURING TEMPORAL LOBE SEIZURES: A SIMULTANEOUS EEG-FNIRS STUDY

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Rationale: Functional near-infrared spectroscopy (fNIRS) is a non-invasive imaging technique of potential value in the study of epileptic patients (1, 2). Its temporal resolution (20Hz) offers the possibility to study the evolution of hemodynamic changes occurring during seizures. We report here on the hemodynamic behaviour observed in a group of patients with mesiotemporal epilepsy (MTLE).

Methods: Patients were diagnosed with MTLE based on multimodal analysis of clinical history, video-EEG monitoring, ictal SPECT, EEG-fMRI, MEG-EEG and intracranial recordings.

EEG-fNIRS recordings were obtained using 19 EEG in-house electrodes (EEG video-monitoring; Compumedics, USA) combined with 68 to 120 NIRS channels (ISS, USA) covering the frontal, temporal and parietal lobes bilaterally. Seizure-onset and seizure-end times were respectively defined as the earliest and latest clinical or electrographic evidence of seizure activity. Hemoglobin concentration variations were calculated using the Modified Beer Lambert Law.

Results: Four patients with MTLE underwent simultaneous EEG-fNIRS recordings (age 19-49 y-o, 2 males/2 females). A total of 8 complex partial seizures from 3 patients were successfully recorded. All seizures showed significant increase of oxyhemoglobin concentration ([HbO]) compared to baseline starting in the temporal regions and then propagating to adjacent regions.

When analyzing the hemodynamic signals during the rising slope (H"8s after seizure onset), ipsilateral temporal [HbO] was higher then the controlateral side in 87% of seizures while ipsilateral temporal deoxyhemoglobin concentration ([HbR]) was lower than the controlateral side in 100%. When analyzing the hemodynamic signals at the peak of [HbO] intensity (H"40s after onset) and as the seizure propagates, areas of maximal [HbO] changes were congruent with the epileptic region in only 50% of seizures.

Time course analysis of [HbR] shows an initial decrease followed by a significant increase (after H"40-60s). The average duration of seizures as determined by EEG was 77s ± 13s while hemodynamic signals returned to baseline after an average of 181 ± 27s.

Conclusions: This study suggests that (a) mesiotemporal lobe seizures are easily detected by continuous EEG-fNIRS; (b) that earliest hemodynamic changes rather than peak changes are more accurate in identifying the region of seizure onset; (c) that the compensatory rise in CBV during seizures may not be enough to respond to the oxygen demand; (d) and that hemodynamic changes take several seconds to return to baseline after the seizure is over.

3.232

RELATIONSHIP BETWEEN INTERICTAL MEG BACKGROUND SOURCE SPECTRAL ANOMALIES AND EPILEPTOGENIC ZONES

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Rationale: We sought to determine whether the sources of interictal MEG background activity can help identify areas of cortical dysfunction in patients being evaluated for epilepsy surgery. We compared source-power topography in different frequency bands to epileptogenic regions that were identified using intracranial EEG recordings.

Methods: We studied seven patients who underwent MEG studies at the Froedtert MEG Center (Medical College of Wisconsin)as part of their presurgical evaluation for epilepsy surgery. All the patients subsequently underwent intracranial EEG studies followed by resection of epileptogenic zones, and had Engel's Class I outcome 6 months post-surgery. MEG recordings were performed using a 306-channel MEG system (Elekta Neuromag, Helsinki, Finland) at a sampling rate of 2000 Hz. Patient-specific head models were constructed by extracting grey matter surfaces from each patient's T1-weighthed MRI volume data using automated segmentation and surface tessellation techniques. Our source imaging method is based on 15,000 elementary current sources constrained to the cortical mantle, with a source separation of about 3 mm. From each patient, between 5 to 7 minutes of awake eyes-closed MEG recording was used for source analysis. All samples of MEG recordings were subjected to automated artifact, EKG, and noise reduction using Signal Space Separation and Principal Component Analysis. Each patient's recording was divided into 2-second long epochs, and frequency-domain distributed source imaging was performed for frequencies from 1 to 500 Hz using weighted L2 minimum norm estimates. The topography of source power in different frequency bands was then compared to areas that were resected in each patient.

Results: Our patients ranged in age from 17 to 46 years (35+/-9.9 years). MR imaging abnormalities were present in 6 of these patients. Seizure origin was frontal in 3 patients, and anterior temporal, temporo-parieto-occipital, medial parietal, and temporo-parietal in one patient each. Source power at low frequencies (delta and theta) showed focal concentration with maxima within the resection zones in five of these patients. One patient had asymmetric focal delta and theta power concentration concordant with a frontal resection area that was dwarfed by biposterior low-frequency power related to posterior slow waves of youth. The last patient showed extensive bilateral temporo-occipital source power in all bands, although surgical resection only included the left anterolateral temporal neocortex.

Conclusions: Cortical sources of low-frequency (delta and theta range) MEG background activity are highly correlated with regions of seizure onset in patients with partial epilepsy. Source imaging of background MEG activity can provide useful information relevant to localizing cortical dysfunction in patients with partial epilepsy, even in the absence of interictal epileptic spikes.

3.233

APPLICATION OF DIFFUSION TENSOR IMAGING IN TEMPORAL LOBE EPILEPSY WITH MESIAL TEMPORAL SCLEROSIS DRUG-RESISTANT: CORRELATION WITH FDG-PET HYPOMETABOLIC AREA

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Rationale: The most common cause of drug-resistant epilepsy is MTLE secondary to hyppocampal sclerosis (HS). In mesial temporal lobe epilepsy (MTLE) the postoperative seizure outcome, in terms of seizure freedom, is about 80%; however up to 20% of patients continue having seizures after surgery.

In order to delineate better the epileptogenic zone in these patients Diffusion Tensor Imaging (DTI) has been used as part of the non-invasive preoperative evaluation of patients with MTLE. This technique has the ability to determine changes in cerebral cortico-subcortical microscopic structure.

The aim of this study was to determine whether DTI could be able to determine the precise location of the epileptogenic lesion in patients with MTLE non-invasively.

Methods: We selected ten patientes with MTLE and HS (5 left, 5 right) who underwent a comprehemsive presurgical evaluation, including FDG-PET. Then each patient in this group was compared to a control group comprised of 30 non-epileptic healthy subjects. For these analysis we used a two samples t-test using SPM8.

Results: There was an increase in mean diffusivity (MD) over the ipsilateral mesial temporal region as well as over the thalamus, the caudate nucleus, and the cingulate and frontal region in all patients. There was also a decrease in fractional anisotropy (FA) over of the ipsilateral insular region and both basal frontal regions, involving the main propagation pathways known in MTLE. There was also a good

agreement between the FDG-PET hypometabolism and the increase in MD.

Conclusions: In conclusion, DTI might be a useful technique for the noninvasive presurgical evaluation in patients with MTLE. In most cases it indicates the location of the epileptogenic lesion, as well as other areas that could be primarily involved in seizure generation and propagation.

3.234

CORPUS CALLOSUM INVOLVEMENT IN PATIENTS WITH EPILEPSY ASSOCIATED WITH HIPPOCAMPAL SCLEROSIS

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Rationale: : Diffusion tensor imaging (DTI) provides information about neural tissue microstructure, specifically, white matter (WM). In experimental studies, repeated seizures produce neuronal damage and cell death. In addition, axonal demyelination, edema, replacement of axons by glial cells, and astrocyte proliferation, may all be associated with seizure induced damage. DTI studies are sensitive to detection WM damage in various disease states. DTI can disclose WM abnormalities in apparently normal regions by conventional imaging, uncovering microscopic pathological changes.

Our objective in this study is to evaluate corpus callosum (CC) fiber integrity in patients with medically refractory epilepsy secondary to hippocampal sclerosis (HS), measuring fractional anisotropy (FA) and apparent diffusion coefficients (ADC).

Methods: Eight HS patients and six healthy controls were studied. Magnetic resonance imaging was performed in a 3.0 T scanner (Achieva Intera, PHILIPS). Region of interest (ROI) analysis was performed in DTI sequences to access FA and ADC measurements. Mean values and standard deviations (SD) were calculated.

Results: Mean FA in the CC was significant reduced in HS patients (0.567; SD: 0.027) compared to healthy controls (0.609; SD: 0.030) (p=0.018). Mean ADC in patients was significant higher (0.876 x 10-3 mm2/s; SD: 0.038 x 10-3 mm2/s) than in controls (0.802 x 10-3 mm2/s; SD: 0.047 x 10-3 mm2/s)(p=0.007).

Conclusions: Those data demonstrate abnormalities in the integrity of the connecting white matter tracts (specifically, CC) in patients with HS associated epilepsy. WM involvement appears to be another at-distance effect of HS. The extent of WM tract abnormalities and its impact on cognitive function and drug refractoriness should be further elucidated.

3.235

COMBINING GRANGER CAUSALITY AND DIFFUSE OPTICAL TOMOGRAPHY TO INVESTIGATE THE EFFECTIVE CONNECTIVITY IN TEMPORAL LOBE EPILEPSY (TLE)

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Rationale: Mapping brain networks allows insight into the brain's functional architecture and physiology and help to better understand and treat TLE. Diffuse optical tomography (DOT) is an emerging functional neuroimaging technique that can simultaneously map both oxy- and deoxyhemoglobin with high temporal resolution. The aim of this study is to reveal directed interactions of activated brain areas in TLE using both the DOT findings and the effective connectivity techniques, such as Granger causality.

Methods: We performed the simultaneously EEG and optical recordings in rats with seizures. Granger causality analysis based on activity-evoked optical change measurements including oxy- and deoxyhemoglobin time courses, is implemented to build a plausible network between different brain regions of interest (ROI).

Results: With the recovered blood volume and blood oxygen parameters, the three-dimensional DOT is able to localize the epileptic foci. The hemodynamic parameters in ROIs are then employed to generate the effective connectivity network, which exploits the time-frequency representation of neural time series to manifest causal relationship in different frequency bands, as well as at different time instants. The simultaneous EEG recordings are also processed to investigate the neurovascular coupling and help interpret the built network.

Conclusions: DOT is gaining acceptable as a technique particularly suitable for routine follow-up in children and unconscious epilepsy patients since it utilizes the noninvasive light to capture the neurovascular and neurometabolic parameters. The Granger causality analysis based on the DOT findings is able to reveal the directed influences between different brain areas. Compared with fMRI, the comprehensive hemoglobin contrasts of DOT enable innovative studies of the biophysical origin of the effective connectivity signal in TLE.

3.236

MAGNETIC RESONANCE SPECTROSCOPY DETECTS NEURONAL DYSFUNCTIONS IN EXTRA-HIPPOCAMPAL REGION IN PATIENTS WITH MEDIAL TEMPORAL EPILEPSY

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Rationale: Magnetic resonance spectroscopy (MRS) allows the in vivo assessment of macromolecules involved in neuronal process, for example, neurotransmitters. Some important differences between MRS and magnetic resonance imaging (MRI) arise from the fact that the primary aim of MRS is to obtain chemical information and that of MRI is to provide spatial information. The temporal lobe epilepsy (TLE) is associated with hippocampal atrophy. Usually MRS is used to help in lateralization of epileptogenic foci, but in this study we used this

Magnetic Resonance technique to test the hypothesis that neuronal loss occur also in other parts of brain.

Methods: 27 patients with clinical diagnosis of Temporal Lobe Epilepsy and 24 healthy volunteers were evaluated. The two groups were matched in age. Images were acquired using a 3 T MR scanner (Achieva, Philips Medical Systems) with a SENSE 8-channel head coil during a single MR imaging session. The spectroscopy data were acquired with a PRESS sequence type (from the English point resolved spectroscopy sequence) in the axial plane with echo time (TE) of 288 ms and repetition time (TR) of 2000. The size of the volume of interest was 80x60x20 mm, positioned on the cingulate gyrus, corpus callosum and surrounding white matter, a region considered as representative of the whole brain. Metabolic concentrations were measured at 2.0 ppm (NAA), 3.0 ppm (Cre) and 3.2 ppm (Cho). Metabolites were assessed as ratios to Cr [NAA/Cr, Cho/ Cr] and in absolute units.

Results: The index NAA/Cre showed a significant difference (p=0,035) between patients (3,42±0,66) and healthy controls (3,02±0,63). But the index Cho/ Cr wasn't significant (p=0,326).

Conclusions: In our patients group, the region of interesting was characterized by a decrease in the NAA concentration, this indicate neuronal dysfunction. These results are consistent with the hypothesis that exist neuronal loss outside the temporal lobe region.

3.237

BONE MINERAL DENSITY IN AMBULATORY PEDIATRIC PATIENTS WITH EPILEPSY

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Rationale: Chronic antiepileptic drug (AED) administration has been shown to have a negative effect on the bone mineralization process. The complex negative effect of AED on bone homeostasis is multifactorial: AED's cause a direct increase in bone turnover as well as an indirect effect on Vitamin D (Vit D) metabolism via induction of cyp450 enzymes. Reduced bone accumulation during childhood, a critical period of mineralization, can have long-lasting consequences on bone health. Factors such as type of medication and body mass index may influence child's risk of decreased bone density.

Methods: A retrospective analysis of a consecutive group of ambulatory pediatric patients evaluated at a specialized epilepsy center was conducted. All patients were on chronic (>1 yr) antiepileptic medication. Thirty two patients had a dual-energy radiograph absorptiometry (DEXA) scans (BMD). The BMI (low: d"18.5, normal: >18.5<25, or overweight:e"25), the AED regimen (at least one enzyme inducing medication or no enzyme inducing mediations) and Vit D levels were recorded.

Results: Twenty five percent of our cohort was diagnosed with low bone density osteoporosis/osteopenia (e"1 SD below the mean for their age group). Of these, about fifty percent were diagnosed with osteoporosis (e"2.5 SD below the mean for their age group). Vit D levels did not appear to influence the bone status: 50% of patients with osteoporosis and 80% of patients with osteopenia had low vit D levels vs. 87% of patients with normal BMD. Findings support a protective effect of high BMI on bone status as observed in adult populations. 61% of patients with normal bone density had high BMI (e"25), compared to 12% in the osteopenic group and none in the osteoporotic group. 75% of patients with osteoporosis and 20% of patients with osteopenia (about half of the patients with low bone density) had low BMI (d"18.5), compared to 9% of patients with normal bone density. AED did not influence the BMD (56% of patients with osteoporosis/ osteopenia were treated with enzyme inducing drugs compared to 73% of patients with normal bone density) although their use was associated with low Vit D. Additionally, Caucasian race seemed to be a risk factor for osteoporosis/osteopenia: 60% of osteopenic patients and 100% of osteoporotic patients were white. This finding is consistent with trends in bone density in the adult population.

Conclusions: Pediatric patients on antiepileptic medication have a high risk for low bone mass and guidelines for regular evaluation of bone status are necessary. Risk factors for low bone density among pediatric epilepsy patients may include low BMI and Caucasian race. Complex factors directly related to epilepsy as a chronic progressive disease (e.g. chronic oxidative stress) may interfere with the bone homeostasis in addition to the low Vit D and AED's.

. Comparing prevalence of patients with low vitamin D level, high and low BMI, AED regimen and race among patients with normal and low bone density.

IMAGE: tables/908318_T1.jpg

3.238

CO-MORBID OBSTRUCTIVE SLEEP APNEA IN EPILEPSY: CLINICAL CHARACTERISTICS AND SEIZURE REDUCTION FOLLOWING NASAL CPAP THERAPY

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Rationale: Co-morbid obstructive sleep apnea (OSA) is frequent in epilepsy. Treatment with nasal continuous positive airway pressure (nCPAP) reduces seizure frequency. However, predictive features enabling triage for polysomnography (PSG) and nCPAP efficacy remain unclear. We aimed to describe clinical characteristics of co-morbid OSA in epilepsy and to analyze the effect of nCPAP therapy on seizure frequency.

Methods: We retrospectively analyzed epilepsy patients with OSA (E+OSA, n=111, PSG apnea-hypopnea index (AHI)>5/hour) and without OSA (E-OSA, n=74) between 1/1/00-5/30/09. Demographic, seizure frequency, antiepileptic drug (AED) load, and PSG variables were recorded. Seizure frequency was compared between E+OSA patients compliant with nCPAP and those who either deferred nCPAP or were non-compliant. Group comparisons were analyzed with 2-tailed T-tests or Wilcoxon signed rank tests in JMP or SAS (Chicago, IL).

Results: PSG yielded OSA diagnosis in 111 (60%). Average AHI in E+OSA was 22.4 ± 20.8. Hypersomnia was more frequent in E-OSA v. E+OSA (95.9% v. 84.3%, p=0.014), although objective sleepiness was no different (mean sleep latencies 12.8 v. 12.2 minutes, p=0.66). Clinical variables that were more frequent in E+OSA than E-OSA were male sex (59.5 v. 37.8%, p=0.004), older age (mean 45.9 v 39.6 years, p=0.0018), weight over ideal (BMI>25, 90 v. 75.7%, p=0.005), enlarged neck (42.6 v. 39.6 cm, p=0.0007), and sleep hypoventilation (36.9 v. 9.5%, p<0.001). Snoring, witnessed apneas, nocturnal seizures, and AED load were similar between groups. 43 patients received

nCPAP. Of 33 patients having pre- and post-nCPAP data, seizure frequency decreased significantly (t=2.138, p=0.04). 79% reported seizure reduction and 61% were responders (50% or greater seizure reduction), and effect held when AEDs were unchanged or reduced (n=18, p=0.01). In untreated patients, there was no difference in seizure frequency (n=28, t=-1.411, p=0.17).

Conclusions: PSG has a diagnostic yield of 60% for suspected OSA in epilepsy patients. Clinical factors associated with OSA include male sex, older age, enlarged neck circumference, and overweight body habitus. The frequency of nocturnal hypoventilation in OSA patients with epilepsy was an unexpected finding requiring further study. Interestingly, epilepsy patients without OSA more frequently reported subjective sleepiness, but were not objectively sleepier, suggesting that seizures, antiepileptic drug load, and other sleep co-morbidities (i.e., periodic limb movement disorder, insufficient sleep quantity, or primary CNS hypersomnia) may also cause sleepiness in epilepsy patients. nCPAP treatment significantly reduces seizure frequency, comparable to or exceeding the effect of adjunctive AEDs. Further prospective studies of the impact of co-morbid OSA on seizure burden and interictal state factors crucial to quality of life (i.e., mood state, vulnerability to AED adverse effects, and sleepiness/vigilance) are warranted.

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PREVALENCE AND PREDICTORS OF OBSTRUCTIVE SLEEP APNEA IN EPILEPSY: DO TRADITIONAL RISK FACTORS MATTER?

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Rationale: Small series suggest that sleep apnea increases the risk of seizures in people with epilepsy; whereas its treatment improves seizure control. The prevalence of obstructive sleep apnea (OSA) measured by polysomnography (PSG) is higher in people with epilepsy, especially medically refractory cases, than the general population (Malow et al., 2000; Manni et al., 2003). However, studies involving a more diverse epilepsy population have not been performed and the role of traditional OSA predictors (age, gender, body mass index [BMI]) has not been thoroughly investigated.

Methods: This is a cross-sectional study involving adult epilepsy patients recruited from a tertiary care epilepsy clinic. Consecutive patients without prior sleep disorder diagnoses were invited to participate. Subjects completed a series of questionnaires including the Epworth Sleepiness Scale (ESS), maintained sleep diaries and underwent PSG with expanded EEG. OSA was defined as an apnea-hypopnea index (AHI) > 5. The association between presence of OSA and AHI with variables including age, gender, BMI, neck circumference, ESS, mean monthly seizure frequency and number of antiepileptic drugs (AEDs) were analyzed using unpaired t-tests and chi-square tests depending on data distribution. Regression models were fit to test the independent effects of these variables on predicting the presence of OSA and AHI.

Results: 132 treated subjects (mean age 38.7+13.2 yrs; BMI 28.9+7.3; male gender 44%) were included. Subjects took a mean of 1.6 (1-4) AEDs and 48.5% were treated with monotherapy. OSA was found in 55 (41.7%) subjects, with 26.5% having mild (AHI 5-<15) and 15.1% having moderate to severe OSA (AHI >15). Age-specific prevalence of OSA was 17.1%, 45.9% and 66.7% in the <30, 30-50 and >50 year-old groups, respectively. No difference was found in overall OSA prevalence in female (39.2%) and male (44.8%). subjects. In subjects over 50 years, OSA prevalence was higher in females (72.2% vs. 58.3%; Figure 1). The distribution of OSA severity was comparable between genders (Figure 2). The prevalence was doubled in obese (BMI >30) compared to non-obese (BMI<30) groups (60.4 vs. 31%) overall, although for subjects over 50 years of age, the prevalence was comparable (68.8 vs. 64.3%). Multiple logistic regression analysis identified age and BMI as significant predictors for OSA.

Conclusions: Our study demonstrates a high prevalence of OSA in a diverse group of epilepsy patients, markedly exceeding that of general population. As in the general population, the prevalence increases with age and BMI. However, in contrast to general population studies, women with epilepsy appear to be at a similar risk as men. Further studies are needed to elucidate the mechanisms underlying the increased risk of OSA in epilepsy patients. These findings support the routine screening for OSA in all people with epilepsy given its potential impact on seizure control and quality of life.

IMAGE: images/906256_A.jpg

IMAGE: images/906256_B.jpg

3.240

SIGNIFICANT REDUCTIONS IN HEART RATE VARIABILITY DURING ICTAL AND POSTICTAL EPISODES IN PHARMACORESISTANT EPILEPSY

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Rationale: Poorly controlled epilepsy is associated with higher mortality compared to the general population. A significant percentage of deaths in epilepsy are due to sudden unexpected death or SUDEP. Although the mechanisms that underlie SUDEP are not clear, possible causes include seizure-related hypoxia and/or cardiac arrhythmia. To investigate whether cardiac autonomic modulation is dysfunctional during and after seizures, we measured heart rate (HR) and heart rate variability (HRV) before, during and after seizures to better understand mechanisms that may underlie SUDEP.

Methods: Twenty-five patients with pharmacoresistant epilepsy were admitted to the UCLA epilepsy monitoring unit for video-EEG recording. Simultaneous EEG and ECG was carried out during complex partial (n=13) and generalized tonic-clonic seizures (n= 12). EEG was manually reviewed to determine the beginning and end of ictal discharges. A semi-automated computer algorithm detected successive QRS complexes in the ECG signal. Time series corresponding to R-waves were manually reviewed to remove artifacts, and linear interpolation was used to correct R-R intervals that deviated more than 20% from the preceding R-R interval. Automated software (Kubios HRV, Kuopio, Finland) was used to compute time- and frequency-domain, and non-linear measures of HRV for each R-R series during the following epochs: immediately preceding seizure onset (preictal), from beginning to end of EEG ictal discharges (ictal), and two consecutive episodes immediately following the end of the seizure (labeled early & late postictal). Repeat measures analysis of variances was used to evaluate HR and HRV in relation to periictal episodes.

Results: The mean duration of ECG analyzed for each episode was as follows (minutes: seconds): preictal: 2:32±0:29; ictal 1:38±0:44; early postictal 2:00; and, late postictal 3:15±0:54. Compared with preictal epochs, the following significant changes were detected during ictal,

early and late postictal periods (% change from preictal): higher HR (61, 34 & 22), reduced RMSSD (-17, -10 & -10), lower sample entropy (-58, -30 & -13), and reduced short-term variability on Poincaré plots (-18, -10 & -11). An increase in long-term variability on Poincaré plots was observed during ictal and early postictal periods (17 & 8%) in relation to preictal periods. Furthermore, a significant reduction in high frequency power (-25%) and higher ratio of low frequency to high frequency power (65%) was observed during ictal episodes compared to preictal periods. No significant differences were detected in SDNN, coefficient of variation R-R intervals, or low frequency power.

Conclusions: These data confirm results from previous experimental animal studies and indicate a significant and robust reduction in vagal-mediated regulation of HR and HRV during ictal and immediate postictal periods. The present study and results from previous patient studies suggest that ictal and postictal dysautonomia and deranged HRV may be critical factors in the lethal events associated with SUDEP.

3.241

ARE CHILDREN WITH EPILEPSY AT HIGHER RISK FOR INJURY? - A PROSPECTIVE STUDY OF INJURY RATES IN CHILDREN WITH EPILEPSY COMPARED TO THEIR NEAREST-AGED SIBLING

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Rationale: To identify whether Children with Epilepsy (CWE) are at higher risk of injury. This information can help us individualize injury prevention advice given, promoting safety, while minimizing restrictions which can affect the child's physical and psychosocial development.

Methods: Prospective cohort study of CWE and their nearest aged sibling. CWE were eligible for study if they (a) were age 3-17 years, (b) had a confirmed diagnosis of epilepsy and were either on AEDs and/or had one or more afebrile seizures in past six months, (c) had no major motor or sensory deficits and (d) had a sibling control in similar age group.

Sibling controls had no history of afebrile seizures, a developmental quotient above 70 and no major motor or sensory deficit.

Parents were asked to complete several screening tools at study onset (Parenting scale and Symptom Inventory for ADHD). Additionally, they were asked to complete monthly injury logs for both the CWE and their sibling and a seizure log for the CWE for 12 months. Additionally, they completed an Activity log for two 2-week periods (study onset and 6 months) for both the CWE and their sibling.

Results: While 150 CWE-Sib pairs were enrolled in the study, only 47/150 (31%) completed some or all of the Injury and Seizure Logs, with 25 pairs completing 6 months or more .Overall, 257 months of data collection was available. CWE did not have significant more injuries than their siblings (271 vs 218, p=NS). Most injuries were minor (e.g. bumps, scrapes, minor burns from deep fryers at jobs) and all injuries requiring medical attention were sports-related. Injuries were most common in CWE in males under age nine (47% of injuries) and in sib controls in females over age ten (46% of injuries).

While 1485 seizures were recorded over the study period in the cohort with epilepsy, the majority of these (98%) occurred in only 10/47 (21%) patients. Only 12/271 (4.4%) injuries in the epilepsy cohort were related to seizures. Additionally, we found no correlation between seizure frequency or number of AEDs taken and injury risk.

Conclusions: CWE are not at significantly greater risk of injury compared to their non-epileptic siblings. Most injuries in the epilepsy cohort were not seizure-related. Surprisingly, the most complex and poorly controlled patients did not have higher risks of injury.

While families should be routinely cautioned about potential risks around water, excessive restriction of activities does not seem warranted for most CWE. Our results are limited by the low response rate in this study and need to be confirmed in larger studies.

3.242

CHILDREN WITH EPILEPSY HAVE INCREASED AROUSAL INDICES ON POLYSOMNOGRAPHY COMPARED TO AGE MATCHED CONTROLS

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Rationale: Various studies have reported increased prevalence of sleep disorders and daytime sleepiness in patients with epilepsy. Studies have also suggested that patients with epilepsy have macrostructure sleep abnormalities. These include increased arousal indices, increased sleep onset latencies, fragmented or reduced REM sleep, increased stage shifts and increased N1 sleep and decreased N2 and N3 sleep in epilepsy patients compared to controls. Most of these studies focused on school aged and teenaged children. However, there is limited data in pre-school aged children with epilepsy.

Methods: We reviewed records of patients with epilepsy who had normal polysomnography. We selected an age matched control group from patients who also had normal polysomnography in our sleep lab. We excluded children with neurological disorders from the control group. The patients and controls were divided into two groups based on their ages: P (preschool aged): 1-5 years; S (school aged): 5 or more years. Fifteen of the epilepsy patients had focal epilepsy, 6 had generalized epilepsy and 3 patients had unknown type of epilepsy. We compared sleep efficiency, % time for stages REM, N1, N2 and N3; arousal indices and sleep latencies on polysomnography of the epilepsy patients with the control group.

Results: We analyzed 24 epilepsy patients and 24 controls. The group P had 7 patients and the group S had 17 patients aged 3 ±1.5 and 10.8±3.6, respectively. The patients in the control group were aged 2.9 ± 1.3 and 11± 3.6, respectively. There was no statically significant difference between the ages in the epilepsy and the control groups. [p =0.89 and 0.87 respectively] For the group P, there was a significant difference in the onset latencies between the epilepsy and the control groups. [Group P: 15.6± 34; Control group: 65.5±36.1; p =0.017] For the group S, there was a significant difference in the arousal indices between the groups. [Group S: 6.8±1.8; Control group: 4.8±1.4; p =0.001] When analyzing all ages together with the control group, we found that the arousal indices were significantly higher for epilepsy patients [p =0.002]. We did not find significant differences for the other parameters. [Table 1]

Conclusions: In our study, we found that older children with epilepsy have significantly higher arousal indices when compared with age matched controls without neurological disorders. In addition, younger children with epilepsy have significantly prolonged sleep latencies, but have no significant change in arousal indices. We did not find significant

differences for the other parameters. Our data suggest that patients with epilepsy are prone to have sleep onset and sleep maintenance problems which could be contributing to daytime sleepiness in these patients. Further study is needed to address this issue.

Table 1

IMAGE: tables/907219_T1.jpg

PSG: polysomnography, SE: sleep efficiency, SL: sleep latency, N1: stage N1, N2: stage N2, N3: stage N3, REM: Stage REM, AI: arousal index

3.243

STATUS EPILEPTICUS REDUCES CARDIAC VENTRICULAR FUNCTION

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Rationale: Status epilepticus (SE), which is a period of protracted seizure activity, produces lasting autonomic abnormalities, lethal cardiac effects, and increased risk of mortality in both patients and animals. Albeit, the mechanisms that increase mortality are unknown, accumulating evidence suggests that excessive stimulation of the sympathetic nervous system (SymNS) during SE contributes to cardiac dysfunction. Neurogenically mediated cardiac stunning is a reversible deficit in cardiac pumping efficiency that can result from adrenoceptor overstimulation by the SymNS. We previously observed cardiac myocyte damage and altered electrical activity of the heart in an animal model of SE. However, functional deficits in cardiac performance after SE have not been previously reported in animals. These studies were designed to determine if self-sustaining limbic status epilepticus (SSLSE) in rats produces cardiac stunning, which is mediated by the SymNS.

Methods: SSLSE was induced in male, Sprague-Dawley rats by electrical stimulation of the left amygdala for 40min. After the first stage 4 (Racine Scale) seizure, rats were divided into 2 groups and administered either saline (SE-Sal) or the peripherally acting, â-1 adrenergic antagonist atenolol (SE-AT; iv, 1mg/kg) that maintained heart rates at pre-seizure levels. SSLSE was terminated after 90 min by valproic acid (ip, 400mg/kg). Control (Cont) rats received similar treatments at concurrent time points, but no electrical stimulation. Following 24hr, rats were anesthetized with urethane (ip, 1.2mg/kg), and implanted with electrodes to record electrocardiographs (ECG), and a catheter in the right carotid artery to measure mean arterial pressure (MAP) and left ventricular performance. QT interval, corrected for heart rate (QTc; Bazett's formula), and dispersion (QTcd) were calculated from the ECG. Cardiac output (CO) was measured by thermodilution. MAP and left ventricular pulse pressures (LVPP) were recorded from the catheter in the aortic arch and ventricle, respectively. LVPP was used to determine ventricular performance by calculating the change in left ventricular max pressure divided by the change in time (dP/dt max).

Results: In SE-Sal animals, CO and left ventricular dP/dt max were significantly decreased, while MAP, QTc, and QTcd were increased when compared with SE-AT and Cont rats 24 hr after seizures. There was no significant difference in heart rate in any group 24hr following SE.

Conclusions: These studies demonstrate diminished cardiac ventricular function in a rat model of SE that is consistent with SE in humans. Further, these studies show that administration of the â-1 receptor antagonist AT during SSLSE prevents the development of cardiac contractile dysfunctions within 24hr of SE. Finally, these data are consistent with the hypothesis that during SE high levels of plasma catecholamines induce adrenoceptor over-stimulation producing cardiac stunning. Together these results provide a therapeutic strategy for the prevention of adverse cardiac effects caused by SE, which may reduce the risk of death.

3.244

TENSION TYPE HEADACHE, MIGRAINE AND OTHER TYPES OF HEADACHE IN EPILEPSY: A MULTIVARIATED ANALYSIS

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Rationale: Epilepsy, headache and migraine are among the most prevalent neurological conditions and these relationships have long been recognized. However there are few controlled studies evaluating at the same time the prevalence of different types of headache in epilepsy. In this study we evaluate the prevalence of different types of headache in adult patients with epilepsy accessing if epilepsy would be an isolated risk factor for these forms of headache.

Methods: Our study is a case-control study evaluating the prevalence of tension type headache, migraine, or other types of headache in 175 patients with epilepsy and 189 respective controls. Neurologists experienced in headache evaluated patients with epilepsy and controls for headache episodes during the previous year. Clinical characteristics, neurophysiological studies and neuroimaging data of patients with epilepsy were also analyzed. Variables studied in both groups, patients with epilepsy and respective controls were sex, age, time at school, and type of professional activity. After univariated analysis, a multinominal logistic regression model was utilized to evaluate if epilepsy would be an isolated risk factor for different types of headache.

Results: In our study, 39% of controls and 75% of patients with epilepsy had history of headache, a significant difference (O.R. = 4.75; 95% CI = 3.04-7.44; p<0.0001). Migraine was present in 17.1% of control individuals and in 40.2% of patients with epilepsy, a significant difference (OR=3.25, IC 95%=1.99-5.30, p<0.001). The frequency of other forms of headaches was slightly higher in patients with epilepsy when compared with control group, but the difference was not statistically significant. After multinominal logistic regression epilepsy emerged as an independent risk factor for tension type headache (O.R. = 6.58; 95% CI = 3.21-13.51; p<0.0001), migraine (O.R. = 5.55; 95% CI = 3.22-9.61; p<0.0001), as well as other types of headache (O.R. = 2.60; 95% CI = 1.39-4.88; p=0.003).

Conclusions: In line with previous findings we observed an increased frequency of headache in patients with epilepsy. Moreover, we observed also that epilepsy was an isolated risk factor for tension type headache, migraine, as well as other types of headaches. Further studies are necessary to elucidate better the different mechanisms involved in the association between epilepsy and tension type headache, epilepsy and migraine, and epilepsy and other types of headaches. However, further studies are also necessary to delineate common mechanisms for different types of headaches in epilepsy. This work was supported by CNPq.

3.245

RISK FACTORS FOR MIGRAINE IN EPILEPSY: A LOGISTIC REGRESSION ANALYSIS

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Rationale: Epilepsy and migraine are among the most prevalent neurological conditions. A comorbidity relationship between epilepsy and migraine has long been recognized. However there are few studies evaluating independent risk factors for migraine in patients with epilepsy. In this study we evaluate independent risk factors for migraine in adult patients with epilepsy.

Methods: A cross-sectional study of 190 patients with epilepsy evaluating independent risk factors for migraine in epilepsy. Neurologists experienced in headache evaluated patients with epilepsy for migraine. Clinical characteristics, neurophysiological studies, neuroimaging data, and pharmachological treatments of patients were included in the analysis. Specifically, variable studied were age at epilepsy onset, time of epilepsy, presence of generalized tonic-clonic seizures, type of epilepsy, seizure control, type of pharmachological treatment, familiar history of epilepsy and familiar history of migraine. After univariated analysis, a binary logistic regression model was utilized to evaluate independent risk factors for migraine in epilepsy. Results were expressed in odds ratio (95% confidence interval) and were considered positive if $p<0.05$.

Results: In our cohort, forty percent of patients with epilepsy had migraine as co-morbidity. Univariated analyis showed that patients with epilepsy that were women, those younger, and those with familiar history of migraine or epilepsy were in risk for migraine. However, after logistic regression analysis only being a woman (O.R. = 3.54; 95% CI =1.75-7.14; $p<0.001$) or having a positive familiar history of migraine (O.R. = 4.50; 95% CI = 1.53-13.26; $p = 0.01$) remained independent risk factors for migraine in epilepsy.

Conclusions: Although several variables have been associated with migraine in patients with epilepsy, few studies have been designed to identify independent risk factors. In our study we observed that being a woman or having a positive familiar history of migraine were independent risk factors for migraine in epilepsy. Our results suggests that gender-related mechanisms and genetic factors are determinant for migraine in epilepsy. This study was supported by CNPq.

3.246

A NEW EPILEPSY SPECIFIC RISK ADJUSTMENT COMORBIDITY INDEX

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Rationale: In health care research, measuring the comorbidity profile of study subjects is essential to the control of confounding when assessing mortality as an outcome. Several comorbidity risk adjustment indices such as the Charlson/Deyo and Elixhauser have been developed utilizing acute care and cancer patients. While these methods have been widely used for risk adjustment, they do not include some important epilepsy related comorbidities. Our goal was to develop an epilepsy specific risk adjustment comorbidity index.

Methods: The following administrative databases were linked (from 1996-97 to 2003-04): a provincial health care insurance plan registry, a hospital discharge abstract database, an emergency room visits database, and a physician claims database in a large Canadian health region (Calgary). Mortality data were obtained from the vital statistics database up until December 2005 to account for delays in mortality coding. A case was defined as anyone who had 2 physician claims or 1 hospitalization or 1 emergency room visit over two years coded for epilepsy. A washout period of at least 3 years (with no epilepsy coding before the index date) was used to ensure that the majority of epilepsy cases were newly diagnosed. A total of 33 comorbidities were assessed for inclusion in the epilepsy specific comorbidity index. A parsimonious model was selected using stepwise logistic regression leaving 14 comorbidities in the final model. Each comorbidity was then assigned a value of 1 to 6 based on the hazard ratio. A total prognostic score was calculated for all eligible subjects using the new epilepsy specific comorbidity index and the Charlson index and crude mortality was compared.

Results: 7,253 subjects met the epilepsy case definition. The mean age was 38 years (range: 0.03-96) with males representing 52% of cases. The mortality rate among this group of epilepsy patients with primarily newly diagnosed epilepsy was 7.9%. High rates of chronic pulmonary disease (20.3%), depression (28.2%) and hypertension (19.6%) were noted. Crude mortality among patients was similar for each prognostic score using either the epilepsy specific comorbidity index or the Charlson/Deyo index. However in most prognostic score categories crude mortality scores were higher using the epilepsy specific comorbidity index than the Charlson/Deyo index. The linear slope for crude mortality by prognostics score was also higher for the new epilepsy specific comorbidity index vs. the Charlson/Deyo index.

Conclusions: A new comorbidity index for epilepsy specifically designed to include clinically relevant and statistically significant conditions provided better discrimination of crude mortality in a population-based group of epilepsy patients. A disease specific comorbidity index should facilitate better control of confounding, better prediction of mortality and may also be of value for predicting health resource use in epilepsy. However, this new epilepsy specific comorbidity index requires further validation in additional populations with longer term follow up.

3.247

KCNQ CHANNELS IN THE NUCLEUS TRACTUS SOLITARIUS OF THE BRAINSTEM MIGHT BE INVOLVED IN SUDEP

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Rationale: Sudden Unexplained Death in Epilepsy (SUDEP) accounts for 10% of epilepsy-related deaths with 85% of these fatalities between the ages of 20-50. Its incidence is about 1/1000 people with epilepsy per year, but is higher in intractable epilepsy. The underlying mechanisms are not well understood, but seizure-induced cardiac and respiratory arrest is the final step. The cardiovascular and respiratory system is subject to precise reflex regulation to ensure adequate oxygen delivery to different organs under a wide range of circumstances. The barosensory and chemosensory afferents send information via cranial

nerves to the nucleus tractus solitarius (NTS), which relays it to higher centers in the central nervous system (CNS). The CNS and NTS integrate this information producing changes in heart rate, peripheral resistance and respiration that maintain arterial pressure and blood gas levels within normal limits. NTS is, thus, positioned at the initial step for of the homeostatic reflex response suggesting a potential critical role in cardiovascular and respiratory regulation during seizures. In the CNS, voltage-dependent Kv7 (KCNQ) K+ channels regulate neuronal excitability by delaying action potentials through the M-current. However, they have not been studied in the NTS. Furthermore, we hypothesize that alterations in M-current at the NTS might contribute to the increased susceptibility to SUDEP in experimental models of intractable epilepsy.

Methods: Glass micropipette electrodes were prepared with a Sutter P-97 puller to resistances of 3-6 MÙ. Recordings were obtained using a HEKA EPC-10 patch clump and PULSE data acquisition system. Currents were low-pass filtered at 0.5-2 kHz, sampled at 0.5-5 kHz, depending upon the experiment. At the amplifier, 40-80% series resistance compensation was applied. M-currents were recorded for a suitable baseline period before application of agonists. We examined the M-current properties from KCNQ channels in NTS neuronal cultures and brain slices of NTS in control and kainic acid treated rats.

Results: We found that KCNQ channels were expressed in the NTS. The M-current in the NTS displays many of the classical characteristics of M-currents recorded from different CNS and peripheral neurons, including the lack of inactivation and slow kinetics. The M-current density in NTS neurons was 4.0 ± 0.2 pA/pF. The M-current in the NTS was also completely blocked by the selective M-channel inhibitor XE991. Since many neurons also display EAG-like currents, which can mimic M-currents, we calculated the time constant of deactivation in these experiments by fitting the current relaxation at -60 mV to an exponential, with a t of 77±14 ms. This value is typical of M currents, but more than six-fold faster than ERG currents (Selyanko AA et al, 1999).

Conclusions: Discovery of M-channels in the NTS opens the door to our exploration of the novel physiological mechanisms responsible for SUDEP.

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3.249

TESTING EPILEPSY CANDIDATE GENES IN AUTISM

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Rationale: Autism and epilepsy are common complex disorders which independently result in significant behavioral and developmental problems. Their co-occurrence is conservatively estimated at 30%. Biologic mechanisms that account for this co-occurrence have eluded discovery. Several conceptual models have proposed a common brain pathology in which autism and epilepsy are independent consequences of the same underlying disorder. Given the overlap in these two disorders we proposed that epilepsy risk genes could be etiologically relevant to autism. The objective of this study was to test the hypothesis that epilepsy related candidate genes may confer risk to autism.

Methods: Using existing genome wide association study (GWAS) data, we examined 33 candidate genes, selected on the basis of previous reports of association or biological relevance to epilepsy or epilepsy and co-occurring autism. The discovery dataset consisted of 438 autism families from the Hussman Institute for Human Genomics (HIHG) autism program genotyped on the Illumina 1M chip. The validation dataset consisted of 457 autism families from the Autism Genetics Resource Exchange (AGRE) genotyped on the Illumina 550K. The 1M Beadchip is redundant to the 550K Beadchip with the addition of approximately 500,000 more SNPs.

Results: We examined single nucleotide polymorphisms (SNPs) in our autism GWAS dataset for each of candidate genes. All SNPs were tested for association to autism using a family based test for association. A finding was declared significant if a SNP was nominally significant in the HIHG and AGRE datasets and showed greater significance in the joint analysis. Two SNPs in CACNA1G (rs11079919 and rs9898731) were significant in the HIHG, AGRE, and joint analyses. Both are in CACNA1G but are in intronic regions and are in high linkage disequilibrium (LD). A third SNP, (rs2240119), while not significant in the HIHG dataset, is significant in the AGRE dataset (p=0.002) and highly significant (9.55E-04) in the joint analysis. Additional analysis of an ASD-epilepsy only dataset (N=71) revealed SNPs of interest in GABRG2, GABRB3, and SCN2A

Conclusions: Testing genes with biological relevance to epilepsy yielded a significant association to SNPs in CACNA1G, a calcium channel gene which has recently been implicated in autism as well as idiopathic generalized epilepsy. The role of ion channel genes in autism risk is supported by evidence showing that calcium channel dysfunction is tied to both non-syndromic and syndromic autism (e.g., Timothy Syndrome, a multisystem disorder characterized by cardiac, immune, and cognitive abnormalities along with a clearly defined autism phenotype). Calcium dependent defects that perturb neural development lead to changes common to those found in autism (e.g., cell-packing density, decreases in neuron size and arborization, and alterations in connectivity. Further, calcium channel variants in autism (e.g.CACNA1G) are tied to increased calcium signaling suggesting a role for calcium dependent activation in this disorder. The role of sodium channel and GABA-ergic variants are also of great interest.

3.250

LONG TERM DEPRESSION OUTCOMES AFTER RESECTIVE EPILEPSY SURGERY

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Rationale: Approximately 20-55% of people with epilepsy suffer from significant mood problems. Resective epilepsy surgery has been associated with improvement in depressive symptoms up to two years post resection. Longer-term results of depression outcomes have not

been studied, prospectively. The depression literature, in patients without epilepsy, shows the five-year risk of depressive relapse is up to 80%. This study explores five-year outcomes using linear mixed effects model, which accounts for time effect adjusting for co-variables.

Methods: Analysis was performed in a sample of 379 adult subjects who were enrolled between 1996 and 2001 in a multi-center prospective study to evaluate outcomes of resective epilepsy surgery. A standardized protocol to record history, neurological evaluation, MRI, video-EEG monitoring, and neuropsychiatric assessments was administered. As part of the standardized protocol, assessment of depression symptoms using Beck Depression Inventory (BDI) was conducted at preoperatively as well as 3, 12, 24, 48, and 60 months postoperatively. Epilepsy control was classified into one of four categories: “excellent” (completely seizure free during the 5-year follow up, “good” (>=2 consecutive years of being seizure free and one or more seizures during the 5-year follow up period), “fair” (seizure free <2 but >= 1 year) and “poor” (never had a one full year of seizure freedom through out the 5 year follow up).

A mixed-model repeated-measures analysis was performed, which adjusted for co-variates of seizure location, pathology, gender, age, race, education, and seizure control.

Results: Out of total 379 patient, 256 patients had both presurgical and 5 year depression evaluations. Of the 256 subjects who were evaluated presurgically, 164 (64.1%) were not depressed, 34 (13.3%) were mildly depressed, and 58 (22.7%) had moderate to severe depression. After five years, out of the 256 subjects who were re-evaluated 198 (77.3%) were not depressed, 20 (7.8%) were mildly depressed, and 38 (14.8%) were moderately to severely depressed (See Figure 1). Of the subjects that had missing data at 5 years: 13 had moderate to severe depression while 94 were not depressed at their last visit, respectively. Subjects who completed 5-year BDI were not significantly different from those who dropped out during follow up in terms of their baseline BDI score, depression status, seizure control, age, gender, education and seizure location.

Five years after surgery, mixed model demonstrated that reduction in mean change from baseline in BDI was greater in excellent seizure control than in fair and poor group (p=.0006 and p=.02 respectively). People with good seizure control had greater reduction in BDI than poor seizure control group (p=0.02), and borderline significance than fair seizure control group (p=0.055). See Figure 2. No significant difference was found among other group comparisons.

Conclusions: While all patients have initial improvement in depressive symptoms post respective surgery, only patients with good or excellent seizure control have sustained long term improvement.

IMAGE: images/904722_A.jpg

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INCREASED IPLA2 ACTIVITY IS A MARKER IN THE HYPPOCAMPUS OF PATIENTS WITH TEMPORAL LOBE EPILEPSY AND PSYCHOSIS

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Rationale: Temporal lobe epilepsy (TLE) secondary to mesial temporal sclerosis (MTS) is the most frequent cause of focal refractory epilepsy in adults. In addition to severe neurological symptoms, these patients present a high prevalence of psychiatric symptoms. The prevalence of schizophrenia-like psychotic symptoms in patients with MTS ranges from 7% to 11% and are thus higher than the expected 1% in the general population. Given the clinical similarities, it is conceivable that psychosis in epilepsy may share some common pathological substrate with schizophrenia. One consistent biochemical finding in schizophrenia is an increased activity of the enzymes phospholipases A2 (PLA2). This family of enzymes is responsible for the metabolism of membrane phospholipids and it is composed by three main groups: cPLA2, sPLA2 and iPLA2. This pioneer study, evaluated the activity of PLA2 subgroups in the hippocampal tissue of patients with refractory TLE with MTS, aiming to ascertain whether patients with TLE-MTS with psychosis have increased PLA2 activity compared to those patients with TLE-MTS without psychosis.

Methods: We determined PLA2 activity by radioenzimatic assays in hippocampal tissue from 7 patients with TLE-MTS and psychosis, as compared to 9 TLE-MTS patients without psychosis. Hippocampal tissue was obtained from subjects who underwent a surgical procedure (anterior temporal lobectomy) indicated due to a therapy-resistant epilepsy.

Results: TLE-MTS patients with psychosis showed a significantly higher brain iPLA2 activity as compared to patients without psychosis (p= 0,016). No significant differences were found between both groups regarding sPLA2 and cPLA2 activities (table). The group of patients with psychosis had somewhat higher mean ages and duration of the illness, but these differences were not significant, and the activities of the PLA2 subgroups did not correlate with age, duration of the disease and frequency of epileptic seizures.

Conclusions: This is the first study that analyses the activity of PLA2 in patients with TLE and psychosis shading a new light in the complex mechanisms that underlie this association. Our findings reinforce the concept of common etiopathogenic mechanisms for psychiatric disorders in epilepsy.

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PREVALENCE AND PREDICTORS OF DEPRESSION IN 2,128 EPILEPSY PATIENTS

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Rationale: Assess feasibility of computer-assisted health status data acquisition in a high-volume tertiary epilepsy center to determine prevalence and predictors of co-morbid depression.

Methods: Subjects included 2,704 patients seen between Nov 2008 and Mar 2010 in a tertiary epilepsy outpatient setting. Patients used touch-screen computer technology to enter responses to standardized surveys of seizure severity and depression: the Liverpool Seizure Severity Scale (LSSS) and the Patient Health Quality-9 (PHQ-9), respectively. Data from one visit per patient were used and included demographics (age, sex, marital status, and race); driving status (driving, not driving, or not driving for reasons other than epilepsy); epilepsy type (focal, generalized, or undefined); seizure control (controlled vs. intractable);

and number of antiepileptic drugs (AEDs) used. The PHQ-9, validated in general medical populations, has been shown to have significant correlation with a DSM-IV diagnosis of major depressive disorder when the total score is >9. PHQ-9 total score for the nine items ranges from 0 to 27. Scores of 5, 10, 15, and 20 represent cutpoints for mild, moderate, moderately severe, and severe depression, respectively. Both univariate and multivariate data analyses were used for independent risk factor determination.

Results: 2,128 patients (79%) completed the PHQ-9. Mean age was 43.8 (median, 42; range, 19-98; SD, 15.7); 54% were female; 83% were white, 13% black and 4% other; and marital status of most patients (89%) was either single or married with the rest indicating divorce or some other marital status. Mean PHQ-9 for the entire group was 6.4 (range, 0-27, median 4). 561 patients (26.4%) had a PHQ-9 score of >9 with 126 (5.9%) scoring in the severe range. Demographic data were complete for all 2,128; data on epilepsy type and seizure control data were available in only 1,827 (84%), seizure severity in 2,067 (97%), number of AEDs used in 2,024 (95%), and driving status in 2023 (95%). Univariate analysis demonstrated significant associations between depression and all variables listed above. Following multivariate analysis only marital status ($p<.0001$), seizure severity ($p<.0001$), and driving status ($p<.001$) retained independent risk factor status. Seizure control showed a trend in this direction, but did not achieve statistical significance ($p=0.0791$). All data are summaried in the Table.

Conclusions: A nearly 80% completion rate supported the utility of touch-screen computer technology for routine health status assessment in epilepsy outpatients. Roughly one-quarter of all patients endorsed at least a moderate degree of self-rated depression (PHQ-9 >9) with only 6% rating themselves as severely depressed (PHQ-9 >19). Only marital status, driving status and seizure severity proved to be independent predictors of depression whereas number of AEDs prescribed, epilepsy type, seizure control, and race did not. Notably, AED burden was not an independent predictor of depression, a finding that contrasts with the FDA's black-box warning. The large number of study patients adds weight to the significance of these findings.

Predictors of depression in 2,128 tertiary epilepsy center patients

IMAGE: tables/906107_T1.jpg

* Does not drive for reasons other than epilepsy

LSSS = Liverpool Seizure Severity Scale

AED = antiepileptic drug

IMAGE: images/906107_A.jpg

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PSYCHIATRIC CO-MORBIDITY IN CHILDHOOD-ONSET EPILEPSY: NEURODEVELOPMENT MAY BE THE KEY

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Rationale: Psychiatric and neurodevelopmental spectrum disorders (PD & NSD) occur more commonly in people with epilepsy than in the general population. Most population-based studies focus simply on the relative frequencies of these disorders. Little is known about clinical characteristics of epilepsy that might distinguish epilepsy patients most and least likely to have these disorders and on the association between PDs and NSDs themselves in people with epilepsy.

Methods: In a community-based cohort study of young people recruited at and actively followed since their initial diagnosis of epilepsy we examined the reported diagnoses of PD and NSD with respect to sex, age at onset and age at interview, type of epilepsy, intelligence, and measures of seizure control based on follow-up calls made 3-4 times per year, accumulated medical records, and an additional interview performed ~9-years after study entry.

Results: Of 501 participating in the 9-y interview, 247 (49.3%) were female. The average age at onset was 5.8y (SD=4.0) and at 9y interview 15.3y (SD=4.2). One or more PDs was reported in 152 (30.3%) including depression (N=67), anxiety (N=25), bipolar disorder (N=6), ADHD (N=104), OCD (N=14), conduct disorder (CD, N=22), ODD (n=5) and schizophrenia (N=2) with 57 (11.4%) having multiple PDs. One or more NSDs was reported in 209 (41.7%) including delay (N=160), language problem (N=112), dyslexia (N=14), learning disorder (N=135), and autism (N=26). Multiple NSDs were reported in N=145. PDs occurred in 58 (19.9%) without and 94 (45.0%) with NSDs ($p<0.0001$). Overall, PDs were not strongly correlated with patient and epilepsy features with the exception of age at interview (<10y, (15.8%), 10-14y (26.7%), 15-19y (35.5%), 20+y (39.5%), $p<0.0001$). By contrast, most patient and epilepsy features were strongly correlated with NSDs. Depression was not associated with NSDs overall and was only weakly associated with dyslexia ($p=0.03$). By contrast, ADHD was strongly associated with NSDs overall and each one individually ($0.0001< p <0.02$). CD and anxiety were associated with some but not all NSDs. In 383 subjects with IQs > 80, 108 (28.2%) had >1 PD, and 97 (25.3%) had >1 NSD. In this subgroup, PDs were present in 19.6% without and 53.6% with NSDs ($p<0.0001$).

Conclusions: Our findings suggest that some of the associations between epilepsy and psychiatric disorders seen in the literature may be mediated through cognitive and developmental disorders which themselves are strongly associated with epilepsy, particularly in children. This does not appear to be the case, however, for depression. Further research in the area of psychiatric co-morbidity in epilepsy should incorporate assessment of cognitive function and presence of NSDs in order to advance our understanding of how and why these various disorders co-occur together.

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THE IMPACT OF PSYCHIATRIC COMORBIDITY ON QUALITY OF LIFE IN CHILDREN WITH EPILEPSY

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Rationale: Children with epilepsy (CWE) have a high burden of psychiatric comorbidity and experience poor long-term psychosocial outcomes. We compared associations of epilepsy severity and chronic comorbidities with child-report and with parent-proxy reports of health-related quality of life (HRQOL) in CWE to determine: 1) if epilepsy severity and chronic comorbidities are differentially associated with HRQOL in CWE, and 2) if parents and children report these associations differently.

Methods: In a prospective, community-based study of newly diagnosed childhood epilepsy, HRQOL of 278 CWE was assessed 8-9 years after diagnosis, using the Child Health Questionnaire (CHQ), a generic HRQOL measure with both child self-report (11 scales) and parent-proxy versions (12 scales). We compared mean child-reported (CR)-HRQOL scores for children with more versus less severe epilepsy, in addition to HRQOL scores of children with and without a chronic comorbidity, using t-tests. More severe epilepsy was characterized several ways: (a) not seizure-free for 5 years, (b) on anti-epileptic drugs (AEDs), (c) complicated (remote symptomatic epilepsy or epileptic encephalopathy), or (d) pharmacoresistant. Chronic comorbidities included (a) neurodevelopmental spectrum disorders (NDS), (b) psychiatric disorders, (c) migraine and (d) chronic medical conditions. We conducted similar comparisons in the parent-proxy reports of the child's HRQOL (PR-HRQOL). Multivariate linear regression was used to assess unique predictors of HRQOL.

Results: Mean age of epilepsy onset was 4.4 (SD=2.6) years; 47% were female. Mean child age at follow-up was 13.0 (SD=2.6) years; 64% were 5-years seizure-free, 31% were on AEDs, 19% had complicated epilepsy, 12% were pharmacoresistant, 39% had a NDS, 25% had a psychiatric disorder, 15% had migraine, and 24% had a chronic medical condition. Epilepsy severity and having a chronic medical condition were generally not associated with CR-HRQOL, but having a psychiatric disorder, NDS, or migraine was. For example, CR-HRQOL for non-seizure free CWE was significantly worse compared to children who were seizure-free on only 1 scale (pd"0.04) while CR-HRQOL for those children with a psychiatric disorder was significantly worse compared to those without a psychiatric disorder on 10 scales (pd"0.03). In contrast, both epilepsy severity and all types of comorbidity were associated with PR-HRQOL. In multivariate analyses, having a psychiatric disorder was the most frequent and nearly exclusive predictor of CR-HRQOL (8 scales; pd"0.02), whereas both NDS and psychiatric disorder were broadly and uniquely associated with PR-HRQOL across multiple scales.

Conclusions: Chronic comorbidities, particularly psychiatric disorders, are more strongly associated with HRQOL in CWE than is epilepsy severity. Even as epilepsy remits, such comorbidities may have a greater impact on HRQOL than epilepsy alone, thereby raising concerns about potential unmet mental health needs of young people with childhood onset epilepsy as they transition to an adult care setting.

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PAI VS. MMPI-2 IN DIFFERENTIATING NES FROM EPILEPSY PATIENTS

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Rationale: Objective personality assessment is commonly utilized in inpatient epilepsy monitoring units to aid diagnosis. This study compared the Personality Assessment Inventory (PAI) and Minnesota Multiphasic Personality Inventory-2nd edition (MMPI-2) in differentiating patients who were ultimately diagnosed with either psychogenic non-epileptic seizures (NES) or epilepsy (ES) in the context of an inpatient hospital admission.

Methods: The two groups (NES: n = 20; ES: n = 24) received their respective diagnoses following a multidisciplinary inpatient video-EEG monitoring evaluation and for the NES group, exclusion of a physiological etiology. No mixed NES and ES cases were included. Each subject completed both personality measures during the same admission and in a counterbalanced manner. Data from six subjects (3 NES, 3 ES) were excluded from further analysis secondary to invalid PAI or MMPI-2 profiles. The two groups were comparable with respect to age, gender, education, and cognitive ability (WAIS-III/WMS-III). The personality profiles were considered diagnostic of NES via T-score > 70 on the PAI SOM scale and modified Wilkus rules for the MMPI-2.

Results: Using chi-square analyses, the overall accuracy rates for the PAI and MMPI-2 were 79% ($p < .001$) and 68% ($p < .05$), respectively. The positive predictive value (PPV) and negative predictive values (NPV) for the PAI were 1.0 and .70, respectively. For the MMPI-2, the PPV and NPV were .72 and .68, respectively.

Conclusions: Overall, our findings indicate that the PAI better discriminates NES from ES patients as compared to the MMPI-2. These results coupled with a number of psychometric, practical, and economic advantages suggests that the PAI is a more useful personality measure for the inpatient epilepsy monitoring unit.

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PSYCHIATRIC DISEASE IN ADULTS WITH OCCIPITAL EPILEPSY: ROLE OF COMPLEX PARTIAL SEMIOLOGY

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Rationale: Patients with occipital lobe epilepsy may have isolated, simple partial seizures or following associated spread of the electrical discharge to neighboring temporal regions, complex partial seizures with or without secondary generalization. Affective disorders are prevalent in patients with epilepsy and adversely impact quality of life, though limited data is available on psychiatric disease in patients with occipital onset seizures. The purpose of this study was to determine whether the semiology of seizures in this group of patients is correlated with psychiatric co-morbidity.

Methods: We retrospectively identified consecutive, adult patients (>17 years of age) with partial seizures of occipital lobe origin confirmed by video-EEG monitoring at the Strong Epilepsy Center between 2000 and the present. Of 20 patients identified, 16 patients participated in a formal interview by a neuropsychologist or psychiatrist as part of their seizure work-up to evaluate for co-morbid psychiatric disease. The other 4 patients had been diagnosed with dementia or developmental delay in addition to complex partial seizures. Twelve patients were female and 4 were male. The mean age at EEG monitoring was 36.1 years (18-69 years). Seven patients had left and 7 had right occipital seizures. One patient had independent left and right occipital seizures, and one had bilateral, simultaneous, occipital onset.

Results: Patients with simple partial seizures only (5 patients) as determined by clinical history and video-EEG monitoring did not have co-morbid psychiatric diagnoses or report psychiatric symptoms of concern. Ten of 11 patients with complex partial semiology of seizures with or without secondarily generalized tonic-clonic seizures had co-morbid psychiatric disease or endorsed symptoms warranting further psychiatric follow-up (p=0.001). Six patients had a history of affective disorders (depression/dysthymia), 3 had anxiety, and 2 were diagnosed

with psychogenic, non-epileptic attacks distinct from their epileptic seizures.

Conclusions: This analysis confirms that affective disorders are also prevalent in patients with occipital lobe epilepsy though within this sample, only in patients with complex partial semiology. The involvement of temporal lobe structures with seizures in these individuals may predispose to underlying affective symptoms. Alternatively these symptoms may represent a reactive component to the social restrictions that are placed on patients with consciousness impairing events.

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SCREENING FOR DEPRESSION AND SUICIDALITY IN AN EPILEPSY CLINIC

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Rationale: The 2008 FDA alert concerning suicidality and antiepileptic drugs has prompted epilepsy care centers to assess related clinical practices. Although the results of the FDA study are controversial, given the prevalence of comorbid psychiatric illness in the epilepsy patient population, routine screening for depression and suicidality has been recommended by experts and legal advisors in the field.

The purpose of the current project is to describe the results of a process for screening all appropriate adult epilepsy patients for depression and suicidality, in an outpatient epilepsy clinic setting.

Methods: Adults patients seen at the Minnesota Epilepsy Group clinic for first-time or routine clinic visits were administered a brief self-report questionnaire. Patients were included if they were over the age of 18, their own legal guardian, and able to read and understand the questionnaire. The questionnaire included the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) and the suicide question from the Beck Depression Inventory-II (BDI-II). Patients were also asked if they were being treated by a psychiatrist, psychologist, or counselor. Clinic nursing staff scored the screening measure and took one of the following actions based on depression symptoms: 1) no response, 2) depression information packet given, or 3) suicide risk assessment administered by psychology staff. Current AED data was collected from each patient.

Results: Since project onset 104 patients have completed questionnaires. The mean score on the NDDI-E was 11.42 (>15 is suggestive of depressive disorder). On the BDI-II suicide question, 95 % responded “I don’t have any thoughts of killing myself” and the remaining 5% responded “I have thoughts of killing myself, but I would not carry them out”. Approximately 1/4 of patients met established criteria to receive a depression information packet, and 72 % had no action taken. No patients required immediate mental health assessment due to indicated suicidal risk. There were no differences in the number of AEDs prescribed to patients scoring >15 or <15 on the NDDI-E. The possible relationship between specific AEDs and depressive/suicidal symptoms will be explored.

Conclusions: A new process for monitoring depression and suicidal symptoms was instituted in a busy epilepsy clinic with minimal disruption to clinic procedures. These findings support existing literature on prevalence of depression in the epilepsy patient population. Based on this limited sample, no clear relationship between AED use and suicidal thinking was observed. Although this project addresses the FDA warning concerns, a more comprehensive assessment of all factors that may contribute to compromised life satisfaction is in the best interest of this patient population

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EPILEPSY AND FAMILY HISTORY OF PSYCHIATRIC DISORDERS IN THE NATIONAL COMORBIDITY SURVEY REPLICATION(NCS-R)

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Rationale: Epilepsy affects about 50 million people globally. Epilepsy and psychiatric disorders share common neurobiologic pathways. There is also a genetic predisposition for the development of some epilepsy syndromes and psychiatric disorders. Prior studies have revealed that people with epilepsy are more likely to develop psychiatric disorders, particularly depression. Some studies have also found psychiatric symptoms preceding the first seizure. The objective of this study was to assess the association of epilepsy with various psychiatric disorders, age of mental health symptom onset, and family history of psychiatric disorders.

Methods: A secondary data analysis was performed of the National Comorbidity Survey Replication (NCS-R) data. The survey was completed by 9,282 English-speaking adult residents of the continental United States between February 2001 and April 2003. There were two parts to the interview. 9,282 respondents completed part-I of the NCS-R. Part II was administered to 5,721 respondents who were asked if a health care professional ever told them that they had epilepsy/seizures and the age of onset. Of these 5,721 people, 2014 individuals were asked about family history of mental illness. Comparisons were performed between respondent subgroups of the following: prevalence of DSM-IV lifetime mental disorders, age of mental health symptom onset, and family history of psychiatric disorders in people told to have epilepsy/seizures.

Results: Of the 5,721 respondents questioned regarding epilepsy, 136 reported a diagnosis of epilepsy/seizures. Of the 2,014 questioned for a family history of psychiatric disorder, 39 reported a diagnosis of epilepsy/seizures. In the NCS-R sample, persons with epilepsy were found to have a higher prevalence of any DSM-IV lifetime disorder, 86.03/100 in people with epilepsy and 76.01/100 in those without, along with an earlier onset of mental health symptoms ($p<0.01$). People with epilepsy had a mean age of mental health symptom onset at 12.69 years,compared to people without epilepsy with onset at 15.04 years. At the DSM-IV group level, only substance abuse and impulse control disorders were found to be significantly higher in people with epilepsy ($p<0.05$). The majority of respondents with epilepsy had onset of mental health symptoms preceding their epilepsy diagnosis. This temporal relationship varied with age of epilepsy diagnosis ($p<0.0001$). Of the psychiatric disorders reported, a statistically significant association was found exclusively between family history of depression and epilepsy. 13/39 people with epilepsy(33.33%) and 399/1975 people without epilepsy(20.55%) reported a family history of depression($p=0.0511$).

Conclusions: Multiple facets of psychiatric disorders appear to be associated with epilepsy. People with epilepsy are more likely to have impulse control and substance abuse, earlier onset of psychiatric symptoms and likelihood of family history of depression. Future research is needed to assess these associations using a larger case

population, in addition to testing the biological pathways of these associations.

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DEPRESSION IN EPILEPSY IS ASSOCIATED WITH LACK OF SEIZURE CONTROL

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Rationale: Depression is common in patients with epilepsy and the strongest predictor of poor quality of life. Depression in epilepsy is under-recognized. Few studies have assessed the association of uncontrolled seizures with depression. We used the neurological disorders depression inventory for epilepsy (NDDI-E), a validated six-item self-report questionnaire, at a tertiary epilepsy center to assess the relationship between depression, seizure control, and antiepileptic drug (AED) usage.

Methods: NDDI-E scores, seizure frequency, and AED usage were recorded in 349 patients. Robust linear regression and logistic regression were used for statistical analysis.

Results: 18.34% of patients had NDDI-E scores >15, consistent with major depression. NDDI-E scores were associated with seizure control ($p<0.001$). NDDI-E scores >15 were more prevalent in patients with seizures in the past month compared with seizure-free patients ($p=0.014$). The odds ratio (OR) was 2.4(95% CI=0.927-6.212) for patients reporting 1 seizure and 2.387(95% CI=1.285-4.434) for those reporting >1 seizure.

NDDI-E scores >15 were more prevalent in patients with seizures in the past 6 months compared with seizure-free patients ($p=0.037$). The OR was 2.804(95% CI=1.014-7.757) for patients reporting 1 seizure and 2.308(95% CI=1.15-4.631) for those reporting >1 seizure.

There was an association between the number of AEDs and NDDI-E scores ($p=0.0005$). The OR for NDDI-E scores >15 in patients taking more than 1 AED relative to patients taking one AED was 2.48(95% CI=1.365 - 4.508).

Conclusions: Major depression is associated with uncontrolled seizures, with a greater than 2-fold increase relative to patients whose seizures are controlled.

NDDI-E Questionnaire

IMAGE: tables/900630_T1.jpg

Circle the number that best describes you over the past two weeks.

IMAGE: images/900630_A.jpg

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SCREENING FOR DEPRESSION IN A TERTIARY ADULT EPILEPSY CLINIC USING THE NEUROLOGICAL DISORDERS DEPRESSION INVENTORY FOR EPILEPSY

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Rationale: Depression is common in patients with epilepsy with reported prevalence of 20-55%. Gilliam et al.(2006) have recently reported that the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is an effective screening tool to detect depression in an outpatient epilepsy clinic setting with NDDI-E scores of >15 associated with a positive predictive value of 0.62. The purpose of this study was to confirm the effectiveness of the NDDI-E in an adult tertiary epilepsy clinic setting.

Methods: The NDDI-E was administered to 63 consecutive patients (29 females) seen in the University of Alberta adult epilepsy clinic. Patients without a diagnosis of epilepsy or with developmental delay were excluded. The mean age of patients was 36 years (range:16-72). Forty-two patients were medically intractable. For patients with NDDI-E scores >12, a detailed interview was performed based on DSM- IV-TR criteria for major depressive episode.

Results: The mean score for medically intractable patients was 14.4 and for seizure free patients was 11.3 (t-test $p=0.003$). No correlation was observed between age and NDDI-E score, nor was any sex difference in score seen. Overall NDDI-E scores were as follows: <13: 30 patients, 13-15: 15 patients, 16-18: 11 patients and >18: 7 patients. Formal DSM-IV-TR depression interview was performed on 28 of 33 patients with NDDI-E scores >12. Four of 28 patients met DSM-IV-TR criteria for major depressive episode (one patient had a NDDI-E score of 18 and the remaining three subjects had scores >18). Positive predictive value for the NDDI-E was 0.14 for a score >12, 0.24 for a score >15 and 0.43 for a score >18.

Conclusions: In contrast to the report of Gilliam et al., the positive predictive value of the NDDI-E with respect to a diagnosis of major depressive episode was considerably lower in our study. While differences in study design and patient populations could have accounted for the discrepancy, our results suggest that further validation of the NDDI-E is necessary in order to develop an effective screening tool for major depressive episodes in epilepsy patients. The overall high NDDI-E scores observed in our study suggest that many epilepsy patients are experiencing symptoms of depression, which may be associated with significant comorbidity despite not fulfilling DSM-IV-TR criteria for major depressive episode.

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ARE AEDS ASSOCIATED WITH SUICIDAL IDEATION?

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Rationale: In 2008, the US Food and Drug Administration issued a warning that antiepileptic drugs (AEDs) result in twice the rate of suicidal ideation as placebo and required a warning in the package insert. Experts in epilepsy, epidemiology, and mood disorders have questioned the strength of the association. We assessed suicidal ideation in children with new-onset epilepsy that subsequently were started on AEDs.

Methods: We recruited 349 children ages 6-14 years with new-onset seizures and prospectively followed them at 18 and 36 months (Austin et al 2010). These children had an estimated IQ of >55 (93%>70) and no complicating pediatric health conditions. AED use was recorded at each follow up. Caregivers completed the Child Behavior Checklist (CBCL) and children > 7.5 years completed the Child Depression Inventory (CDI). For this study we looked at question 91 (Talks about killing self - never vs. sometimes/often) on the CBCL and question 9 (I do not think about killing myself vs. I think about killing myself but I would not do it/I want to kill myself) on the CDI. The association of suicidal ideation with AED use was assessed by Chi-square or Fisher's exact test.

Results: Data from CBCL was available on 337 children at baseline, 297 at 18 months, and 276 at 36 months. Parents reported suicidal ideation in 7.2%, 6.4%, and 3.3% of children at baseline, 18 months, and 36 months respectively. There was no association between suicidal ideation on the CBCL and AED use at any time. CDI was available on 226 children at baseline, 264 at 18 months, and 271 at 36 months. Suicidal ideation was reported by 25.8% of children at baseline, 21.2% at 18 months, and 14.4% at 36 months. When we restrict to those children not on AEDs at baseline, there were increased thoughts of suicide among children currently taking an AED at 18 months compared to children not taking an AED(39% vs. 15%, p=0.003). However, by 36 months, though more children on AEDs reported suicidal ideation (24% vs. 13%), the association was not significant. No suicide attempts or completed suicides occurred during the 36-month period.

Conclusions: The prevalence of suicidal ideation reported by children is higher than that described by parents and is similar to the 20% prevalence reported by Caplan et al. (2005). Suicidal ideation was highest at baseline prior to substantial exposure to AEDS. However, we did find an initial association between AEDs and suicidal ideation at 18 months that weakened at 36 months. Given the frequency of suicidal ideation and the potential association with AEDs, clinicians should monitor for suicidal ideation and psychopathology to reduce risk for the child and to promote quality of life.

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PSYCHOSIS IN TEMPORAL LOBE EPILEPSY: RIGHT-SIDED MESIAL TEMPORAL SCLEROSIS AND LONGER DURATION OF EPILEPSY ARE RISK FACTORS

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Rationale: Patients with partial epilepsy, mostly with temporal lobe epilepsy due mesial temporal sclerosis (MTS), present a higher incidence of mood disorders and psychosis, when compared both to general population and to other epileptic syndromes. Determination of electroclinical profiles that could help predict the occurrence of psychiatric disorders (PD) in these patients might have a positive impact on their treatment and prognosis. Our study aimed to identify electroclinical risk factors for the occurrence and type of psychosis in a group of patients with mesial temporal sclerosis (MTS).

Methods: The study included patients with epilepsy and uni or bilateral MTS, and excluded patients with: other lesions besides MTS, double pathology, or extratemporal ictal onset. All patients underwent psychiatric evaluations (structured questionnaire) and were classified according to DSM IV and ICD 10. Clinical epilepsy variables were: onset age, duration, presence of TCGS, seizure frequency, polytherapy, previous status, complex febrile seizures and laterality (determined by MRI) and epileptogenic zone (determined by interictal and ictal EEG).

Results: We evaluated 63 patients (34 [47.2%] male) with mean age of 39,1 years. Left MTS occurred in 35 (48.6%), right MTS in 32 (44.4%) and bilateral MTS in 05 (6.9%). Out of these 27 (37.5%) presented mood disorders, 23 (31.9%) psychosis. Thirty-four (47.2%) patients were on psychoactive medications. Previous or current PD were absent in 22 (30.55%). Patients with psychoses had longer duration of epilepsy (mean 32.21 ys) when compared to controls (26.26 ys) and patients with depression (24.76 ys) (p=0.046). EEG epileptiform activity on right temporal lobe (p=0.024) were significantly associated with an increase risk for psychosis. Other clinical variables did not differ among groups.

Conclusions: This study confirms that patients with MTS have a high prevalence of mood disorders and psychosis and displayed differences in the electroclinical profile. Most patients with MTS and psychosis presented right-sided changes in both MRI and EEG (interictal and ictal findings). Although correlations between laterality and PD are controversial, the present study is relevant because other possible factors, related to the development of such disorders were taken into account. Longer duration of epilepsy was related to MTS with psychosis, a finding in accordance with at least two current theories explaining this comorbidity.

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ROLE OF ANXIETY AND SLEEP DISORDERS FOR OVERALL QUALITY OF LIFE IN PEOPLE WITH EPILEPSY AND CONTROLS

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Rationale: Epilepsy can negatively affect quality of life (QOL) and increase risk of psychosocial problems. Although seizure frequency is an important determinant of QOL, other social and psychological factors have also been implicated. Co-morbidities such as depression, anxiety and sleep problems are increasingly under investigation. All these factors are known to be predictive of impaired QOL and common among people with epilepsy (PWE). In this study, we examine prevalence of anxiety and sleep disorders in PWE, and their relative contributions to overall quality of life.

Methods: Questionnaires were mailed to two UK samples: a tertiary clinic population (n = 550) and members of the patient organisation, Epilepsy Action (EA; n = 1000). Additionally, EA members could complete questionnaires on-line. Questionnaires were also distributed to an opportunity sample of controls without epilepsy. Questionnaires contained previously validated scales to assess levels of anxiety, sleep disorder, adverse drug effects, felt stigma, levels of social support and clinical and socio-demographic features. Questionnaires were returned by 196 clinic patients, 751 EA members and 297 controls. Data were analysed using regression techniques.

Overall QOL was assessed using Andrews & Withey's 'terrible-delighted faces' scale (7-point scale, best-worst QOL); anxiety by the Speilberger State-Trait Anxiety Inventory (40 items, 20 'state', 20 'trait'); sleep problems by the Pittsburgh Sleep Quality Index (19 items, subjects scoring >5 classified as 'poor' sleepers); and the Epworth Daytime Sleepiness Scale (8 items, subjects classified as 'normal' or 'needing special advice').

Results: The epilepsy samples differed in terms of their clinical status, the clinic sample being more likely to have experienced multiple seizures in the previous year ($p<0.001$), a higher average number of seizures per month ($p<0.001$), earlier age of seizure onset ($p=0.024$), polytherapy ($p<0.001$), and other long-term co-morbidities ($p<0.001$). Only 50% of PWE assessed overall QOL as positive, compared with 75% of controls; a third described it as negative, compared with 14% ($p<0.001$). In a univariate analysis, factors predictive of overall QOL were: general health, health compared to 1 year ago, seizure worry, long-term health problems other than epilepsy, other (non-antiepileptic) medications, state and trait anxiety, social support, stigma and sleep problems. No clinical factor other than patient-perceived seizure control was important; nor were any socio-demographic factors other than marital status. The only factors remaining significant in a multivariate analysis were general health, trait anxiety, night-time sleep quality and social support.

Conclusions: Clinical epilepsy factors contributed little to QOL, whereas wider health and social factors were important contributors. Our data suggest that with appropriate inputs, people with epilepsy can maintain a good QOL in spite of clinical adversity.

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A 2-YEAR PROSPECTIVE STUDY OF PSYCHIATRIC COMORBIDITY IN CHILDREN WITH RECENT ONSET EPILEPSY

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Rationale: At baseline, children aged 8-18 with recent onset idiopathic epilepsy (<12 months since diagnoses) were noted to exhibit learning problems and ADHD (Hermann et al., 2006; Jones et al., 2007). These children were re-evaluated following a 2-year interval to monitor the trajectory of their psychiatric comorbidity.

Methods: Participants were 66 children with recent onset epilepsy and 57 healthy cousin controls with a mean age of 14 years at follow-up. Children participated in the follow-up evaluation 2 years after the baseline evaluation. At baseline and follow-up, all participants and their parents underwent a standardized psychiatric interview to characterize DSM-IV diagnoses using the K-SADS. Learning problems were defined as special education, assistance in reading and math, mandatory summer school, tutors or grade retention. Based on the baseline diagnoses, children were placed into the following groups: healthy cousin controls, epilepsy-no ADHD or learning problems (epi-), epilepsy with learning problems and no ADHD (epi+LP), epilepsy with ADHD (epi+ADHD). Based on the follow-up interview, DSM-IV diagnoses were examined in the following categories: interval and current diagnoses.

Results: At baseline among the children with epilepsy, 30 (45%) children were epi-, 17 (26%) children were epi+LP, and 19 (29%) children were epi+ADHD. In terms of diagnoses that were present during the 2-year interval, 25% of controls met criteria for any DSM-IV disorder, as well as 53% of the epi-, 53% of the epi+LP, and 100% of the epi+ADHD ($p = 0001$). When current diagnoses were examined at follow-up, 19% of the controls, 33% of the epi-, 47% of the epi+LP, and 84.2% epi+ADHD met criteria for any DSM-IV disorder ($p = 0001$).

Conclusions: In this study we followed children with recent onset epilepsy who were subdivided into groups based on the presence or absence of learning problems or ADHD at baseline and evaluated DSM-IV diagnoses over time to identify any changes. All children with epilepsy, regardless of their baseline status, did not demonstrate progression over time in terms of interval and current psychiatric diagnoses evaluated at the 2- year follow-up. The presence or absence of learning problems or ADHD does not appear to negatively impact psychiatric comorbidity over time.

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POSTICTAL EXACERBATION IN SEVERITY OF INTERICTAL PSYCHIATRIC SYMPTOMS WORSENS SIGNIFICANTLY THE QUALITY OF LIFE OF PATIENTS WITH EPILEPSY

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Rationale: Postictal psychiatric symptoms are defined as symptoms that occur within 120 hours of a seizure. Often there can be a symptom-free period between the seizure and the onset of psychiatric symptoms. Symptoms identified in the postictal period can be restricted to the postictal period or can represent an exacerbation in severity of interictal symptoms. Whether having interictal symptoms only, postictal symptoms only or postictal exacerbation of interictal symptom affect differently the quality of life of patients with epilepsy is not known. The purpose of this study is to answer this question.

Methods: 50 consecutive patients with pharmaco-resistant partial epilepsy were included in the study. The postictal period was defined as the 72 hours following a seizure. Interictal psychiatric disorders were identified with the structured psychiatric interview MINI International Neuropsychiatric Interview developed to generate DSM-IV current diagnoses. During the previous 3 months, we established the presence of: (1) postictal psychiatric symptoms only: (2) interictal symptoms only; (3) interictal symptoms with postictal exacerbation in severity. To that end, we used a structured interview, the Rush Postictal Psychiatric Symptoms Questionnaire (RPPSQ). Only postictal symptomatology that occurred after more than 50% of seizures was included. The quality of life was measured with the Quality of Life in Epilepsy Inventory-89 (QOLIE-89). Statistical analyses consisted of ANOVA and linear logistic regression.

Results: 34 patients had a DSM-IV diagnosis, 30 of whom met criteria for a depressive (n =6), anxiety (14) or both (n =10) disorders. 35 patients (70%), reported interictal symptoms with postictal exacerbation in severity with or without other postictal symptoms, while six patients (12%) had only postictal symptoms.

The mean (±SD) total QOLIE-89 score dropped from 53.6(±7.4) among patients without interictal or postictal psychiatric phenomena to 39.5(±10.9) among patients with interictal symptoms with postictal exacerbation in severity with or without other postictal symptoms, while there was no difference in the scores of patients with only postictal symptoms [53.5(±6.1)] ($F = 10.9$, $df = 2$, $p<0.0001$). The logistic regression model identified two independent predictors of poor quality of life: 1) The presence of an interictal mood and/or anxiety disorder ($p = 0.017$) and (2) the presence of interictal symptoms of depression, anxiety and neurovegetative symptoms with postictal exacerbation in severity with or without other postictal symptoms ($p < 0.0001$).

Conclusions: While these data confirms the negative impact of interictal depressive and anxiety disorders, it demonstrates that the postictal exacerbation of interictal symptoms further worsens their quality of life. Furthermore, having only postictal psychiatric symptoms does not appear to affect the quality of life, unless they occur together with interictal symptoms that worsen in severity postictally. Whether these latter symptoms respond to pharmacotherapy is yet to be established.

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SEEMINGLY SIMILAR BUT ESSENTIALLY DISTINCT: COMPARISON OF CLINICAL AND PARACLINICAL CHARACTERISTICS IN PATIENTS WITH EPILEPTIC SEIZURES AND PSYCHOGENIC NON EPILEPTIC SEIZURES

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Rationale: Psychogenic non epileptic seizures (PNES) constitute a common diagnostic and therapeutic challenge. Prompt identification of these patients would allow timely administration of psychotherapy and psychopharmacology and prevent diagnostic uncertainty and potentially hazardous, ineffective treatments. We attempted to clarify the differences between patients PNES and epileptic seizures (ES).

Methods: Patients admitted to the Epilepsy Monitoring Unit (MGH and BMC) and outpatient Epilepsy clinic (DUT) completed questionnaires about their social situation, epilepsy, cognition (MoCA), psychiatric state (Beck's Depression, Beck's Anxiety Inventory), sleep (Sleep Apnea, Epworth Insomnia Scale) and quality of life (QOLIE-31). AED levels, EEG recordings and brain MRI scans were obtained. The patients were dichotomized in ES and PNES based on their EEG recordings. Comparison between the two groups was performed using t-test/Mann-Witney test for continuous variables and Chi-Square/ Fischer's exact test for categorical variables that were normally/not normally distributed respectively.

Results: 77 patients with ES and 17 patients with PNES were enrolled. Comparison between the two groups is depicted in table 1. In summary, there was a statistically significant difference between the gender (55.84% of ES vs 100% of PNES were female, $p<0.001$), the marital status (55.84% of ES vs 23.53% of PNES were single, $p=0.02$), the age of onset of epilepsy (16.16+/-11.24 for ES vs 23.76+/-9.83 in PNES, $p=0.01$), the number of AEDs (68.83% >1 AED in ES vs 23.53% < /1 in PNES, $p=0.001$), the level of anxiety (mean score of 11 in ES vs 18 in PNES, $p=0.02$), the degree of insomnia (mean score 14.67+/-6.68 in ES vs 9.94+/-6.91 in PNES), their EEG (64.86% in ES vs 11.76% in PNES were abnormal, $p<0.001$) and MRI findings (64.86% in ES vs 23.53% in PNES were abnormal, $p<0.002$). There was also a trend in the employment status (49.33% in ES vs 75% in PNES were employed, $p=0.06$) and duration of the disease (16.2+/-9.02 in ES vs 11.53+/-9.05 in PNES, $p=0.06$). No statistically significant difference was identified in the other clinical [i.e. sociodemographic (e.g. race, education, living situation), disease related (e.g. compliance, number of seizures), cognitive (MoCa), psychiatric (Beck's Depression), sleep (Sleep Apnea) and quality of life (QOLIE-31)] or paraclinical [AEDs levels] characteristics.

Conclusions: Patients with ES have distinct clinical and paraclinical characteristics from those with PNES. In comparison to ES, PNES appear to be more frequent in women, their bearers are commonly married and employed, they get afflicted by them later in life and suffer from them for a shorter period, they are on fewer AEDs, they have higher levels of anxiety, and they have more frequently normal radiological and electrographic work up. These differences may facilitate not only better identification of patients with PNES but also highlight the importance of evaluating and treating psychiatric comorbidities related to this group of patients.

Table 1: Results

IMAGE: tables/907593_T1.jpg

*2-sided t-test

**Chi-square

***Fisher's exact test

§Mann-Whitney's U test

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OUTCOMES OF TRAUMA-INDUCED PSYCHOGENIC NONEPILEPTIC ATTACKS TREATED WITH EYE MOVEMENT DENSENSITIZATION AND REPROCESSING

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Rationale: Because of high rates of trauma (44-100%) and abuse (23-77%) among PNEA patients, it has been suggested that PNEA are a clinical expression of a PTSD subtype. Although little is known about psychological treatments that are most effective with PNEA, EMDR has proved to be an effective treatment for trauma and is now showing promise in the treatment of PNEA patients with trauma and abuse histories. This presentation details outcomes of 74 patients with PNEA, the majority of whom have such histories, who have been referred for mental health treatment.

Methods: This study integrates EMDR into the mental health treatment of PNEA patients referred after video EEG monitoring confirmed the presence of psychogenic attacks and diagnostic interviews revealed virtually ubiquitous trauma and abuse histories/ experiences. Data were analyzed for patients referred over a 6-year period from a hospital-based clinic serving Floridians and persons from the southeastern US.

Results: The study protocol was comprised of 2-3 initial sessions for diagnosis and rapport building followed by weekly EMDR ranging from 3 to 15 sessions. Of 74 patients referred, 31 were from distant locales and were matched with mental health practitioners in their home locations. 43 patients were interviewed; 20 were seen for consultation only - they refused treatment, preferring to pursue disability benefits. 21 of 23 remaining had trauma and abuse histories. 14 of those realized complete remission of PNEA with EMDR; 8 discontinued treatment because of relocation, transportation difficulties, and the like. Followup reveals no return to seizure status.

Conclusions: EMDR appears to be an efficacious intervention in the psychological treatment of PNEA patients with trauma histories. A two year highly innovative single center randomized controlled tial comparing EMDR with another innovative promising approach, Neurofeedback Therapy (NFT) is planned for the fall of 2010 for 60 patients.

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DEPRESSION IN ELDERLY PATIENTS WITH EPILEPSY

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Rationale: Depression is a common comorbid condition in people with epilepsy. Although epilepsy is one of the most common neurological disorders of old age, few studies have addressed depression in elderly patients with epilepsy. The aim of this study was to evaluate risk factors for depression in geriatric epilepsy patients

Methods: We identified 43 epilepsy patients in our practice age 55 and older who completed neuropsychological testing including the Beck Depression Inventory (BDI), Beck Depression Inventory-Second Edition (BDI-II), and Geriatric Depression Scale (GDS). Thirty-two patients fulfilled criteria for depression. Following variables were evaluated: handedness, age of onset of epilepsy, type of epilepsy (generalized vs. partial), lateralization and localization of seizure focus, duration of epilepsy, treatment resistance, marital status, education, proximity to family, family and personal history of depression or other psychiatric disorders, and temporal relation between onset of depression and epilepsy.

Results: In our sample 16/32 patients (50%) fulfilling criteria for depression reported to be treated for depression. 6/32 (19%) of patients reported having symptoms of depression prior to diagnosis of epilepsy. Patients with depression were more likely to have partial epilepsy (29/29 vs. 9/11, P value 0.018). Although there was a trend for depressed patients to be treatment resistant this was not statistically significant (14/32 vs. 2/10, P value 0.332). Other variables showed no statistically significant difference.

Conclusions: Our data suggest that the majority of geriatric patients developed symptoms of depression after the diagnosis of epilepsy. Partial epilepsy was associated with increased risk for active depression in elderly in our sample. Active patient-doctor communication is crucial in the detection of depression within the treatment of geriatric epilepsy as timely treatment of depression may influence the outcome of both epilepsy and depression.

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COMPARING STANDARD MEDICAL CARE FOR NES IN LATIN AMERICA TO NORTH AMERICA

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Rationale: Standard Medical Care (SMC) for psychogenic nonepileptic seizures (NES) was described in North America (NA). We sought to compare diagnostic and treatment practices in NA to Latin America (LA). Based on the prior NA survey, we hypothesized that a. NA uses more technology to diagnose, and therefore can explain the diagnosis with more assurance, thereby referring patients with NES off to mental health providers; and b. neurologists in LA, will follow and treat NES and comorbidities more often than NA neurologists.

Methods: A survey on diagnosis and treatment practices for NES was administered to 117 practicing clinicians in LA. Results were compared to results from 317 NA clinicians. We used a significance level of alpha=0.005.

Results: Hypotheses tested involved:

1. Diagnosis: NES diagnosis is made by inpatient video EEG/LTM in 88% of NA respondents, compared to 28% of LA respondents, $p<0.0001$. Less than half of LA respondents (47%) reported having vEEG available, compared to 95% of NA respondents, $p<0.0001$; however, when comparing the LA centers with access to any vEEG (including outpatient short term or ambulatory with video), there were no differences in the proportion using vEEG for NES diagnosis, $p<0.0166$. In line with the hypotheses, the diagnosis of NES is made by history and exam alone at twice the rate in LA (38%) than NA (16%), $p<0.0001$.

2. Disposition: Once the diagnosis of NES is made, 73% of NA respondents, compared to 85% of LA respondents refer for treatment by psychiatrist, $p=0.0052$; 39% of NA respondents, compared to 29% of LA respondents reported that neurologists continue to follow, $p=0.0609$.

3. Etiology: The etiology of NES is attributed to trauma/abuse in 43% of NA respondents, compared to 8% of LA respondents, $p<0.0001$. The highest frequency attributable cause of NES among LA respondents was anxiety, reported by 37% of respondents.

4. Treatment: Presumed treatments included relaying the diagnosis, psychotherapy, psychopharmacotherapy, AEDs, other and “do not know”. All categories were equivalent with similar percentages between NA and LA, except for psychopharmacotherapy. A higher proportion of LA respondents (64%) endorsed psychopharmacotherapy to be of benefit than NA respondents (32%), $p<0.0001$.

5. Medications: Just under half of LA and NA respondents prescribed psychotropics when a psychiatric comorbidity to NES was identified. LA respondents (49%) were no more likely to prescribe psychotropics than NA respondents (47%), $p=0.7106$. A higher proportion of NA respondents (83%) discontinued AEDs if lone NES was diagnosed than LA respondents (68%), $p=0.0010$.

Conclusions: Neurologists in NA are more likely to use inpatient vEEG than LA, but this may be a function of a lesser availability of this diagnostic tool in LA. NA and LA see treatments as equally effective, however, more LA endorsed pharmacotherapy to be of potential benefit. More NA neurologists discontinue AEDs with a lone NES diagnosis than LA respondents. This cross cultural multisite survey appears to show some differences in evaluation and management of NES between NA and LA.

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TONIC GABAERGIC INHIBITION IN THE BASOLATERAL AMYGDALA IS HEAVILY MEDIATED BY á5 SUBUNIT-CONTAINING RECEPTORS, AND IS REDUCED IN A MOUSE MODEL OF FRAGILE-X SYNDROME

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Rationale: Fragile-X Syndrome (FXS), caused by a mutation in the Fmr1 gene and subsequent dysfunction of its gene product FMRP, is the leading cause of inherited mental retardation. Patients with FXS display symptoms of commonly comorbid disorders involving network hyperexcitability such as autism, anxiety disorders, and ADHD. In addition, at some point in their childhood up to 25% of FXS patients will have epilepsy. Therefore, the study of FXS provides a platform to investigate common mechanisms of epilepsy comorbidities in a system in which these comorbidities innately occur. To this end we chose to focus our studies on the basolateral amygdala (BLA), a region of interest central to dysfunction in epilepsy and its comorbidities of anxiety disorders, autism, and ADHD. According to our recent studies in Fmr1 KO mice, this brain region shows decreased phasic GABAergic inhibition coupled with principal excitatory neuron hyperexcitability in vitro. This hyperexcitability can be rescued with gaboxadol, or THIP, a superagonist at extrasynaptic, ä-subunit-containing GABA receptors, in the acute BLA slice, indicating a possible role of tonic GABAergic inhibition in controlling BLA excitability. Additionally, hyperactivity of Fmr1 KO mice is reduced in vivo by gaboxadol. This study aims to characterize both the ä- and á5-subunit mediated contributions to tonic GABAergic inhibition in the BLA, and their role in controlling BLA neuron excitability specifically in a mouse model of epilepsy and its comorbidities.

Methods: We utilized single and paired whole-cell patch clamp recordings in acute coronal brain slices to investigate tonic GABAergic currents in principal excitatory neurons and interneurons in the BLA of wild-type and Fmr1 KO mice. Bath and local application of SR95531 (gabazine, 50 ìM), the ä-subunit agonist, THIP (10 ìM), and the á5 inverse agonist, á5IA (1.5 ìM), were used to examine total and relative subunit contributions to tonic currents in BLA neurons.

Results: We report physiological deficits in both á5- and ä-subunit mediated tonic inhibition of principal and inhibitory neurons in the Fmr1 KO BLA versus wild-type. Furthermore, we observed a major contribution of the á5-mediated component to the total tonic current observed in principal neurons and some interneuron subclasses. á5-subunit mediated tonic inhibition specifically also displayed marked outward rectification.

Conclusions: Our results indicate decreased tonic GABAergic currents in BLA neurons of Fmr1 KO mice. Additionally, the rectification of á5-containing GABA receptors implies that tonic currents mediated by these subunit-containing receptors may provide strong control over changes in membrane potential close to firing threshold compared to tonic inhibition mediated by ä-containing receptors, and therefore may be a relative target to control BLA hyperexcitability associated with epilepsy and its comorbidities.

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THE RELATIONSHIP BETWEEN MOOD AND ANTIEPILEPTIC DRUG SIDE EFFECTS IN PATIENTS WITH EPILEPSY

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Rationale: In the last decade many new anti-epileptic drugs (AEDs) were introduced to the market, especially for patients with medically refractory epilepsy. However, as with any medication, side effects are commonly reported upon initiation of treatment with a new AED. Although these side effects may reflect actual physiologic reactions to the drug, psychological factors also significantly affect a patient's reaction to new medication. The "placebo" effect can work both ways, in promoting a positive response to new therapy or in reflecting perceived side effects in patients with psychological difficulties. The current study examines the effects of mood disorders on reported side effects to AEDs in an epilepsy sample.

Methods: A cross-sectional analysis was done to determine the relationship between the side effect profile and respective BDI & BAI scores. Subjects referred for neuropsychological testing were included. Their side effect profile was derived from our review of systems (ROS) collected at each visit. The side effect profile was divided into 4 categories: cognitive/coordination (i.e., dizziness), mood/emotion, sleep, cephalgia , systematic complaints (i.e., rash/eye pain) which was based on the commonly used Adverse Effect Profile (Gilliam, 2003). BDI (n=59) and BAI (n=54) scores were categorized into 4 quartiles. Individuals in the 1st and 4th quartiles were included (those missing ROS were excluded). The number of AEDs was factored into the analysis. Chi squared and t tests were performed where appropriate

Results: There was a significant difference in the mean BDI and BAI scores between the 1st and 4th Quartile ($P<0.05$). Between the 1st and 4th Quartile, there was a significant difference in mood, sleep, cephalgia and systemic complaints for the BDI groups, and cognition/coordination, mood, sleep and cephalgia for the BAI groups. These differences remained significantly different after controlling for the number of AEDs (see table for additional statistical findings).

Conclusions: Patients with high BAI/BDI scores had significantly more symptoms than patients with lower BAI/BDI, even after controlling for the number of AEDs. The spectrum of symptoms however differed between the two groups. Though there was an overlap between mood, sleep, and cephalgia, patients with high BDI scores had elevated systemic symptoms and patients with high BAI scores had elevated cognitive/coordination symptoms (which are the "traditional" AED side effects), but not vice versa. It is possible therefore that the higher symptomatology in depressed patients is driven by somatization, where the higher symptomatology in anxious patients is driven to a larger degree by sensitivity to AED side effects. The oft-heard dictum to go "low" and "slow" when dosing AEDs may be especially true for this latter group, and simple mood screening tools like the BDI/BAI may be useful to obtain before initiating AED therapy. Future analysis will explore how these symptoms change over time, and if there is any relationship to introduction or alteration of AED therapy.

Table of Additional Statistics

IMAGE: tables/908185_T1.jpg

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PAROXYSMAL NON-EPILEPTIC EVENTS IN THE ELDERLY: A VIDEO-EEG REVIEW

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Rationale: Although extensive data of paroxysmal non-epileptic events (PNEE) is available in adult patients, less is known of PNEE in the elderly. The purpose of this study was to compare clinical characteristics of PNEE in elderly and non-elderly adult patients.

Methods: We retrospectively review data of patients aged 60 years or older admitted to the Epilepsy monitoring unit from January 2005 to December 2009. A control group of adult patients with ages between 20 and 45 years with recorded PNEE was used for comparisons. PNEE were classified as physiological or psychogenic. Psychogenic PNEE were classified as follows: 1) Bilateral motor movements, 2) Focal motor events, 3) Transient unresponsiveness or reduced responsiveness; 4) Predominantly sensory or autonomic events. Physiological PNEE included syncope, sleep disorders, movement disorders, transient ischemic attacks, and migraine headaches. We also reported whether patients were or not taking anti-epileptic drugs (AEDs). Significance levels were set at 5%. A Bonferroni correction was made and significance was identified when p d".0071. All analysis were conducted using SAS® v9.2.

Results: In total, PNEE only was recorded in 35 (24.5%) out of 143 patients aged 60 years or older. Mean age of elderly patients was 68.2 ± 7.5 years and mean age of non-elderly patients was 33.3 ± 7.7 years. The age of onset of PNEE was 62.2 ± 11.1 years and 29.6 ± 8.6 years in elderly and non-elderly adults, respectively. In the elderly group, 57.1% were female and in the non-elderly group, 80% were female. No differences (p = 0.132) were found in the type of psychogenic PNEE: 17 (48.6%) elderly and 18 (51.4%) non-elderly patients had bilateral motor movements; 2 (5.7%) elderly and 1 (2.9%) non-elderly patient had focal motor movements, 3 (8.6%) elderly and 10 (28.6%) non-elderly patients had transient unresponsiveness; 5 (14.3%) elderly and 5 (14.3%) non-elderly patients had predominantly sensory or autonomic events. Seven (20%) elderly and 2(5.71%) non-elderly patients had physiological PNEE, including syncope, non-epileptic myoclonus, orthostatic tremors, intoxication, and migraine headache (p = 0.15). We found 26 (74.3%) elderly and 9 (25.7%) non-elderly patients aware and responsive during the PNEE. Significantly (p< .0001) more elderly patients were responsive when compared to non-elderly patients. The estimated percent of elderly patients responsive during the PNEE remained significant (p = 0.0015) after adjustment for gender differences. No differences were found between groups regarding the duration (p = 0.18) or frequency (p = 0.48) of PNEE. Most elderly (74.3%) and non-elderly (71.4%) patients were taking AEDs and no differences (p = 0.78) were found between groups.

Conclusions: Elderly patients were more likely to be responsive and following verbal commands properly during the PNEE than non-elderly adult patients. We did not find any other differences in semiology, duration, or frequency of PNEE between these two age groups. More than 70% of elderly and non-elderly patients were taking unnecessary AEDs.

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VALIDITY OF A DEPRESSION SCREENING INSTRUMENT FOR YOUTH WITH EPILEPSY (YWE)

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Rationale: Depressive symptoms in YWE continue to be under-recognized and under-treated. Only <"1/3 YWE with comorbid psychopathology receive mental health care. Further, seminal papers encourage assessment for depression and suicidality beginning at initial epilepsy diagnosis and urge comorbidities must be treated to increase quality of life for YWE. Despite these recommendations, Gilliam (1) reports that 80% of neurologists do not routinely screen for depression in patients with epilepsy and developed the NDDI-E to increase adult screening. In light of the discrepancy between prevalence rates for depressive symptoms in YWE and diagnosis and treatment of these symptoms, we performed a study to 1) modify the NDDI-E screening tool for youth (NDDI-E-Y), 2) validate the NDDI-E-Y, and 3) facilitate access to mental health care providers and assess barriers.

Methods: Basic demographic and seizure-related information was collected on all participants. 31 YWE were administered the NDDI-E-Y a second time, an average of 15 days later. The NDDI-E-Y has 11 items, with responses 'always/often', 'sometimes', 'rarely', and 'never', given scores of 4 through 1, respectively. Individual item scores for 1st and 2nd testing were compared using weighted kappa statistics. Sums of total scores were compared using Spearman correlation. YWE were referred for further evaluation if e" 7 items were endorsed as 'always/often' or item 6 ('I'd be better off dead') was endorsed - this was dichotomized into 'yes/no' for referral, and 1st and 2nd testing compared using kappa statistic. Finally, total score was dichotomized into greater than 27 or not, and 1st and 2nd testing also compared.

Results: Participants taking a retest of the NDDI-E-Y were 61% female, 71% white and 29% black, ranged in age from 10 to 17, with average age of 15 years. 84% were taking 1 or 2 antiepileptic medications and 2 had a VNS. Most youth had partial epilepsy with impairment of consciousness (68%), with 25% having generalized nonconvulsive epilepsy, and the remainder having generalized convulsive epilepsy. The mean total score was 23 on the initial test, and 22 on the retest. Kappa scores of individual items ranged from 0.16 to 1.00, with an average of 0.48. Two items with perfect agreement were 'I feel guilty' and 'I have difficulty finding pleasure'. Spearman correlation of initial and retest total scores was 0.71 (p<.0001). Scores dichotomized for referral had a kappa value of 0.65, showing good agreement. Total scores dichotomized at score of 27 had a kappa value of 0.89, showing excellent agreement.

Conclusions: Initial results are promising and require further refinement and testing. Further analysis on the 93 youth will compare NDDIE-Y results with the Depressive Disorders module of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present (K-SADS-P). The NDDIE-Y may provide an efficient way to screen for depressive symptoms in YWE. Previous research has indicated early identification and intervention can lead to prevention of depression. A brief tool to use in the clinic setting would be an innovative way to begin this process.

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PREVALENCE OF ANXIETY AND SLEEP DISORDER IN PEOPLE WITH EPILEPSY AND CONTROLS AND CONTRIBUTING FACTORS

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Rationale: The impact of epilepsy on everyday life cannot be solely attributed to seizure frequency. Studies of psychosocial effects of epilepsy highlight the prevalence of anxiety and sleep disorder in people with epilepsy (PWE), even though their relationship with epilepsy is not fully understood. There is a need to raise awareness of these problems so that due consideration can be given to them when prescribing and evaluating treatment regimes.

Methods: Questionnaires were mailed to two UK samples: a tertiary clinic population (n = 550) and members of the patient organisation, Epilepsy Action (EA; n = 1000). Additionally, EA members could complete questionnaires on-line. Questionnaires were also distributed to an opportunity sample of controls without epilepsy. Questionnaires contained previously validated scales to assess levels of anxiety, day/night-time sleep disorders, adverse drug effects, sense of stigma, levels of social support and key clinical and socio-demographic features. Questionnaires were returned by 196 clinic patients, 751 EA members and 297 controls. Data were analysed using correlation and regression analyses.

We used the Speilberger State-Trait Anxiety Inventory (40 items, 20 state, 20 trait) to assess intensity of symptoms; the Pittsburgh Sleep Quality Index (PSQI; 19 items, subjects with global score >5 classified as 'poor' sleepers) to assess night-time sleep quality; and the Epworth Sleepiness Scale (8 items, subjects classified 'normal' or 'needing special advice') for daytime sleepiness.

Results: The epilepsy samples differed in their clinical status, with the clinic sample significantly more likely to have experienced multiple seizures in the previous year ($p<0.001$), a higher average number of seizures per month ($p<0.001$), earlier age of seizure onset ($p=0.024$), polytherapy ($p<0.001$) and other long-term co-morbidities ($p<0.001$). Prevalence of both state and trait anxiety was similar for both samples and significantly higher than for controls ($p<0.001$ for both). Prevalence of daytime sleep problems was 40.9% in the clinic sample, 38.1% in the patient organisation sample, and 23.7% in the control group ($p<0.001$); and of night-time problems was 67.1%, 79% and 62% respectively ($p<0.001$). Factors predictive of state anxiety were: general health, health compared to 1 year ago, seizure worry, level of social support, night-time sleep quality and age. For trait anxiety, important factors were: general health, age at first seizure, seizure worry, day and night-time sleep problems, social support, age and gender. PSQI scores were predicted by other long-term co-morbidities, other (non-AED) medications, adverse drug events and state but not trait anxiety.

Conclusions: Management of PWE requires a holistic approach addressing these wider patient-reported problems, as well as epilepsy-specific ones. Study findings will be disseminated to healthcare professionals, for consideration when establishing treatment regimes and management policy.

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COMMUNICATING THE DIAGNOSIS OF PSYCHOGENIC NONEPILEPTIC SPELLS IS A TRICKY BUSINESS

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Rationale: Psychogenic nonepileptic seizures (PNES) are common cause of refractory spells. PNES are seen in 10 to 58% of adult patients with intractable spells. Video-EEG monitoring has allowed PNES to be effectively distinguished from epileptic seizures. Once the diagnosis of PNES is established, neurologists face the challenge of explaining to the patients that they do not have epilepsy, but that their seizures are a manifestation of psychological distress. Patients may not always receive the "good news" well, leading to poor follow-up outcome. The aim of this study is to evaluate how effectively patients receive and perceive the diagnosis of PNES.

Methods: This prospective study was conducted in the Vanderbilt eight-bed epilepsy monitoring unit (EMU). Adult patients with newly confirmed PNES were included. A self-administered questionnaire was given to patients after the attending physician had communicated the diagnosis of PNES and after receiving written consent. The questionnaire consisted of 41 item Likert-style scaled questions developed by the EMU staff. The questionnaire included items asking if the diagnosis of PNES was clearly communicated and how patients perceived this new diagnosis.

Results: A total of 65 patients were recruited, 46 females and 19 males. All patients had their typical spells recorded on video-EEG (range 1-12, mean 2.18). Thirty three patients had high school education while 27 patients had college education. Sixty one patients (94%) were satisfied with the diagnosis of PNES. However four patients (6%) were not satisfied with the diagnosis. Eight patients (13%) did not agree that PNES has a psychological cause. Twelve patients (20%) thought that diagnosis will not change the outcome. Seventeen patients (28%) thought that the EMU doctors had no clue of the cause of PNES. Thirty three patients (51%) thought that people perceive their spells as fake. Twenty two patients (34%) felt that a diagnosis of nonepileptic spells means being crazy. Nineteen patients (30%) thought that there was no hope for cure of their spells.

Conclusions: Majority of patients (51%) with PNES in our sample did not perceive the diagnosis of PNES correctly. We speculate that this may have bearing on a poor outcome. Significant numbers of patients with PNES also feel that there is no hope for cure of their spells. Proper and thorough education about PNES and preferably earlier diagnosis may prevent this miscommunication and result in better outcomes. A comprehensive approach including psychological counseling, psychiatrist input and effective follow-up may be helpful.

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INDEPENDENT PREDICTORS OF ANXIETY DISORDERS IN TEMPORAL LOBE EPILEPSY: A CROSS-SECTIONAL STUDY

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Rationale: Neuropsychiatric disorders are comorbidity in epilepsy. However, few studies have evaluating independent risk factors for anxiety disorders in epilepsy. In this study we identify independent risk factors for anxiety disorders in temporal lobe epilepsy.

Methods: Cross-sectional study of 124 patients with temporal lobe epilepsy. All patients were submitted to Structured Clinical Interview for DSM Disorders (SCID) for psychiatric evaluation. Additionally, all patients were also submitted to an additional structured interview to collect variables associated with epilepsy or neuropsychiatric disorders. We review medical records of patients like age, gender, family history of epilepsy and psychiatric disorders, duration of epilepsy, control of seizures, presence of aura, history of initial precipitant insults, abuse of substances, neuroimaging and interictal EEG features.

Results: In our study, thirty patients (24% of the total of patients with temporal lobe epilepsy) had anxiety disorders. Generalized anxiety disorder was the most frequent anxiety disorder observed, encountered in 40% of patients with anxiety disorders. Phobias were present in 36% of patients, panic disorders or panic attacks were observed in of 23% of patients, posttraumatic stress disorders were observed in 13% of patients and obsessive-compulsive disorder was present in10% of patients with anxiety disorders. Using univariated analysis we observed that being a woman, having positive family history of psychiatric disorders and having a life-time history of humor disorder were significantly associated with an increased risk for affective disorders in patients with temporal lobe epilepsy. After logistic regression, positive family history of psychiatric disorders (O.R=3.47; 95% CI=1.32-9.09; p=0.01) and a life-time diagnosis of humor disorder (O.R=2.70; 95% CI=1.05-6.94; p=0.04) remained isolated risk factor for anxiety disorder in temporal lobe epilepsy. Sex (woman) showed a statistical trend for being a risk factor for anxiety disorder in temporal lobe epilepsy (O.R=2.88; 95% CI=0.94-8.57; p=0.06). In our study an algorithm constructed based in the binary logistic regression model was able to predict correctly the presence or absence of a lifetime anxiety disorder in 77.4% of patients with temporal lobe epilepsy.

Conclusions: Our results are in line with some studies published previously. However, we identified a positive family history of psychiatric disorders, a positive history of humor disorder, and possibly sex (being a woman) as independent predictors of anxiety disorders in temporal lobe epilepsy. Further studies are necessary to better understand how these factors merge together to generate anxiety disorders in patients with temporal lobe epilepsy. This work was suported by CNPq.

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BEHAVIORAL ATTENTION AND PREFRONTAL DOPAMINE RECEPTOR DENSITY IN THE RAT PERINATAL HYPOXIA MODEL OF EPILEPSY

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Rationale: Children with epilepsy are more likely to develop Attention Deficit Hyperactivity Disorder (ADHD) than children without epilepsy, but it is unknown whether seizures can cause changes consistent with ADHD, such as impairments in visuospatial attention or loss of prefrontal cortex (PFC) dopaminergic receptors. In the current study, these correlates of ADHD were assessed following transient perinatal hypoxia in rats to determine whether early life seizures can alter visuospatial attention and dopamine receptors in the PFC.

Methods: Male and female Sprague Dawley rats received hypoxia on postnatal day 10-12 by lowering O_2 to 5-7% by infusion of N_2 gas into an airtight chamber. After 12 min, O_2 was lowered by ~1%/min. Animals were monitored for seizures, and removed from the chamber upon apnea. Control animals were kept in the same chamber under normoxic conditions. Two weeks later, animals were perfused and brains were processed for immunocytochemistry. Coronal sections labeled with DRD4 antibody, to identify D4 dopamine receptors, were incubated in fluorescent secondary antibody, and the PFC was imaged using a Leica SP2 laser scanning confocal microscope. The number of DRD4 immunopositive receptors per unit volume was quantified using offline measurement software (Imaris).

A second cohort of animals was tested for attention using the 5-arm maze. Animals were partially food deprived during the six phase testing period. During Phase l (habituation), all five arms were baited, illuminated and remained open. During Phases ll, lll and lV (acquisition) the number of arm choices gradually increased with one arm lit and baited. During Phases V and VI (visuo-spatial attention), all doors remained opened and one arm was lit for a duration of 2sec (Phase V) and 0.5, 1 or 2sec (Phase VI), during a 10sec (Phase V) or random (5-35sec, Phase VI) delay.

Results: Initial anatomical measures from a subset of animals (n=6) show a tendency for DRD4 receptor density in the PFC to be reduced following perinatal hypoxia ($t(4)=2.77$, $p=0.056$).

Repeated measures analysis of task acquisition showed a significant main effect for phase ($F(3,36)=52.94$, $p<0.05$), and a significant phase by condition interaction ($F(3,36)=3.19$, $p<0.05$), which showed that the rate of task acquisition was faster for hypoxic animals than for controls (n=14). When the task was switched to a measure of attention (Phases V and VI), there was a significant main effect for condition ($F(1,4)=9.52$, $p<0.05$), with hypoxic animals making significantly fewer errors than controls (n=6).

Conclusions: Together, these results suggest that the PFC dopaminergic system and visuospatial attention are altered by early life seizures in this model, but not in the ways that were predicted. While initial anatomical evidence does support a decrease in PFC DRD4 density, more animals will be needed to confirm this finding. However, behavioral measures showed a surprising result that hypoxic animals outperformed controls in basic task acquisition and measures of visuospatial attention. Interpretations and follow-up data will be discussed.

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CO-MORBIDITY IN PATIENTS WITH PSYCHOGENIC NON-EPILEPTIC ATTACKS

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Rationale: Psychogenic Non-Epileptic Attacks (PNEA) are frequently associated with psychiatric co-morbidity. Co-morbidity with epilepsy has received attention, though knowledge of general medical conditions

is more limited. We sought to characterize the medical co-morbid profiles of patients with PNEA at the time of diagnosis.

Methods: Records were retrospectively reviewed from 26 consecutive PNEA patients at a single tertiary care epilepsy center in Florida. All patients received a final diagnosis of PNEA following video-EEG monitoring interpreted by an epileptologist (WOT). All patients were identified while on the EMU and were evaluated by a psychiatrist experienced in PNEA. Demographics, medications on admission, outcome with respect to neurological and psychiatric diagnoses, and medical co-morbidities were examined. The presence of medical conditions was examined for their prevalence.

Results: A total of 26 (15=female; mean age=40.4) consecutive records were reviewed. A mean exposure to 4.4 AEDs and 3.5 psychiatric medicines were noted on admission. Of 19 patients who had inpatient psychiatric consultation, there was no statistical difference between the 89.5% with self-reported mood disorder compared to 84.2% that received a formal Axis I diagnosis (p=0.783). 15/19 (78.9%) patients reported depression and 7/15 (46.7%) had an Axis I diagnoses of the same. 7/19 (36.8%) reported anxiety and 5/7 (71.4%) had the same Axis I diagnosis. In only 1/19, the inpatient psychiatric diagnosis differed from the outpatient psychiatrist's impression and in only 1/26 (4%) case did recommendations for medication change.

PNEA patients had an average of 5.3 non-psychiatric diagnoses and there was no gender-specific difference between the average number of comorbid medical conditions (p=0.8691). Patients above the age of 40 had on average 6.9 other medical co-morbidities; patients below age 40 had 3.3, respectively (p=0.0129). Most (N=17) reported diagnoses that were based upon subjective symptomatology; 7/26 (26.9%) had chronic pain; 3/26 (11.5%) irritable bowel syndrome, 3/26 (11.5%) sleep apnea, and 2/26, (7.69%) fibromyalgia. In this cohort, 19.2% of the patients had co-morbid epilepsy. Of the 26 patients 16 (61.5%) had at least one comorbidity and 4 (15.4%) had > 1 conditions. Potential objective medical conditions were reported in (3/26) were compared to subjective diagnoses (15/26), the difference was significant (p=0.0096).

Conclusions: In-patient psychiatric consultation rarely changed existent diagnosis or treatment. >60% of patients with PNEA report medical co-morbidities, more were > 40 years of age, and nearly 2/3rds based upon subjective symptoms with chronic pain the most common reported condition.

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PSYCHOGENIC NONEPILEPTIC SEIZURES IN CHILDREN: AGE-RELATED RISK FACTORS AND CLINICAL FINDINGS

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Rationale: Psychogenic nonepileptic seizures (PNES) are episodes similar to epilepsy that are not accompanied by abnormal electrical activity in the brain. Underdiagnosis of this pathological condition has great impact over the children's health. Risk factors are assumed to be similar to those observed in adults. In addition, semiology of PNES in children has been poorly described, but appears to be different from that reported in adults, especially in younger children.

Methods: We performed a review of medical records and video-EEGs of 44 patients under 18 years with diagnosis of PNES confirmed by VEEG. Patients were categorized into semiologic groups according to the main characteristics of their episodes:i. generalized motor activity, ii.focal motor activity,iii.behavioral changes, iv. aura-like symptoms, and v.unresponsiveness. Patients with both epilepsy and PNES were also characterized as mimicking or not their own seizures. Classical indicators (ictal eye closure, pelvic thrusting, stuttering) of PNES in adults were also investigated.

Results: Out of 44 patients (52.3% boys), with a median age of 12.6 yrs (SD + 3.6),

four patients were younger than 6 yrs,16 patients were aged between 7-13 yrs and 24 were older than 13 yrs. Considering age-differences, frequency of boys was higher (2.4 m:1 f) in patients younger than 10 years while the opposite was observed in older (1 m: 1.7 f). Mood disorders were present in 13 (29.5%). Epilepsy was diagnosed in 31 (72.7%) patients. Family history of epilepsy was reported in 47.4% and psychiatric disorders in 58.8%. History of physical and sexual abuse occurred in 18.2% and psychological abuse in four patients (9.1%). Inadequate family setting was detected in 29.5%.Generalized motor activity was the most common type (49.4%), followed by unresponsiveness (29.5%). Behavioral change (6.8%), aura-like (4.5%) and focal motor activity (4.5%) were less frequently observed. There was no significant difference in semiology between younger (< 10 ys) and older children, but the older children presented more prominent motor activity and more unresponsiveness while subtle motor activity occurred more often in the younger children. Among the 44 patients, only one closed her eyes during the seizure and merely two presented pelvic thrusting. Stuttering, tongue laceration and weeping were not observed. Of the 32 patients with epilepsy, 12 mimicked their own seizures.

Conclusions: Adolescents are at higher risk for PNES, although it may occur in younger children. Girls represent a risk group only in older ages, and gender-correlation is not observed in younger children. Mood disorders, personal and family history for epilepsy were predictors of PNES. Inadequate family setting was more relevant than abuse, contradicting what is observed in adults. Semiology of PNES in our group was different from that described in adults. An age-related difference was observed as to type of motor activity. Moreover, classical signs such as ictal eye closure and pelvic thrusting were not reliable indicators of PNES in children.

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THE TEDDY BEAR SIGN DOES NOT INDICATE THE PRESENCE OF PSYCHOGENIC NON-EPILEPTIC SEIZURES

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Rationale: Up to 30% of adult patients presenting with seizure-like episodes are found to have psychogenic non-epileptic seizures (PNES). A review of video footage of patients in a seizure monitoring unit concluded that the presence of a toy stuffed animal, sometimes referred to as a "teddy bear sign", could help identify patients with PNES (Burneo et al., Neurology 61:714-715, 2003), but the usefulness of this sign has been questioned (Hoerth et al., The Neurologist 14:266-270, 2008). We were not certain that the suggested correlation was present in patients in our Epilepsy Monitoring Unit (EMU), and therefore reinvestigated this.

Methods: We studied all patients admitted to the EMU at the Johns Hopkins Hospital during a 12 month period for the presence or absence of a stuffed animal. We de-identified patients according to requirements of the Johns Hopkins Institutional Review Board and recorded age, gender, seizure diagnosis, and presence or absence of mental retardation.

We excluded patients under the age of 15 years, with mental retardation, with diagnoses other than epilepsy or PNES (syncope, sleep disturbance, no events recorded, etc.), or with both epilepsy and PNES.

Results: During a 12-month period, 302 patients were admitted to the EMU and 226 were over 14 years of age. Final diagnoses were epileptic seizures (n = 108), non-epileptic seizures (n = 76), epilepsy and PNES (n = 6), other events (n = 32), and epilepsy with mental retardation (n = 4). Therefore, 184 patients (127 women and 57 men) were studied. Twenty-seven (15%) of these patients brought toy stuffed animals to the epilepsy monitoring unit. Nine patients (7 women) with stuffed animals were diagnosed with PNES and eighteen (14 women) were diagnosed with epileptic seizures (p = 0.4042, two-tailed Fisher's Exact Test).

Conclusions: In this study, the percentage of patients over 14 years of age with stuffed animals in the EMU did not significantly differ between those with epilepsy and those with PNES. In fact, there were more epilepsy patients than PNES patients with stuffed animals. There was an increased percentage of women with stuffed animals. This most likely reflects social norms.

IMAGE: tables/905297_T1.jpg

* Nonsignficant (NS), p = 0.1493, Fisher's Exact Test

** NS, p = 0.4042, Fisher's Exact Test

*** NS, p = 0.4876, Fisher's Exact Test

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LIFE-THREATENING NON-EPILEPTIC SEIZURES: REPORT OF TWO CASES

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Rationale: The differential diagnosis between refractory seizures and non-epileptic seizures is often difficult and requires dedicated investigation, comprising extensive VEEG monitoring. Although most cases are somewhat refractory to medical treatment alone, requiring psychotherapy and a dedicated psychiatric follow-up, they are usually considered benign when compared to epileptic seizures, as they do not lead to physical trauma. We report two cases of potentially life-threatening non-epileptic seizures.

Methods: The authors report two different cases of patients diagnosed with non-epileptic seizures who attempted suicide following the disclosure of their diagnosis.

Results: Case 1: A 48 year-old female patient with a history of refractory epilepsy was admitted to our VEEG monitoring unit for diagnostic clarification of spells. A previous brain MRI disclosed a left perimesencephalic cistern lesion and she underwent surgical removal in another hospital; pathological diagnosis was of an epidermoid cyst. Following surgery there was an increase in seizure frequency, which led to admission to a VEEG monitoring unit at that first hospital and a diagnosis of non-epileptic seizures. Prior to her admission to our unit a new MRI disclosed a lesion similar to the one that had been supposedly removed. She remained refractory to medical treatment and was referred to our service. During a 48-hour VEEG five events were recorded, all of which had the semiological features compatible with non-epileptic seizures. No epileptic seizures were recorded. The patient received the diagnosis of non-epileptic seizures in a comprehensive setting and was sent for psychiatric treatment, as well as following-up with our service in an out-patient setting. She attempted suicide by introducing sewing needles in her anterior thoracic wall, which resulted in cardiac tamponade that was surgically treated with a pericardiac window and drainage. This suicide attempt occurred following a widespread media-coverage of an infant who had been a victim of attempted murder by his step-father, who drugged him and then inserted 31 sewing needles under the baby's skin. Following that, she reported having previously attempted suicide on another occasion.

Case 2: A 30 year-old female patient with a history of refractory epilepsy was admitted to the VEEG monitoring unit, during which she recorded twelve non-epileptic seizures. Her EEG activity was otherwise normal, with no epileptic paroxysms. During her stay she attempted suicide twice, the first time by ingesting 12 pills of Phenobarbital, which as treated with gastric drainage and supportive care. The second time she attempted to jump out of a window of the fourth floor, but was contained and transferred to a psychiatric hospital.

Conclusions: Even though some physicians would dismiss non-epileptic seizures, considering them to be less threatening than epileptic-seizures, sometimes the psychopathology leading to the development of non-epileptic seizures can be so disturbing as to make these events potentially life-threatening.

IMAGE: images/906505_A.jpg

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AGITATION IN EPILEPSY PATIENTS MONITORED WITH INTRACRANIAL EEG

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Rationale: Agitation is characterized by excessive motor or verbal activity, irritability, threatening gestures, and, in some case, assault. Agitation is a common behavioral emergency associated with high risk of injury to patients and health care professionals. As epilepsy surgery is increasingly offered to patients with extra-temporal, non-lesional epilepsy, invasive subdural monitoring will continue to play an important role in determining the epileptogenic zone and adjacent functional eloquent cortex. Complications associated with intracranial monitoring are believed to be independent of the depth electrode technique or type of invasive EEG. No data are available on the corresponding risk of agitation in this patient population

Methods: A retrospective chart review of adult and pediatric epilepsy patients with intracranial EEG monitoring in the Cleveland Clinic Epilepsy Center Epilepsy Monitoring Unit (EMU) between January 2008 and April 2010. The lead author (AD) reviewed the records to identify episodes of agitation and any interventions necessary to calm the agitated patient. The degree of agitation was quantified from written descriptions using the Riker Sedation-Agitation Scale (SAS). Potential causes of the agitation were identified from patient records. Multiple logistic regression was used to identify independent risk factors for the development of agitation in this patient group

Results: During the study period, 170 patients underwent intracranial EEG monitoring. Behavior consistent with any degree of agitation (SAS score 5-7) was documented in 20 patients (11.7%). Severe or dangerous agitation (SAS 6 or7) was documented in 17 patients (10%). At least one episode of agitation was documented in 3 of 15 SDG (13.3%), 12

of 84 SDG +depths (14.2%) and 6 of 42 SEEG patients (14.2%). The documented causes of agitation were post-ictal event (14 of 20, 70%), subdural hematoma (1, 5%) and unspecified (5, 25%). A significant correlation between agitation and Axis II diagnosis (p<0.29,95% Cl-1.2-37%) and older age (p<0.39,Cl-1-2.1%) was noted.

Conclusions: In this retrospective review, agitation developed in 11.7% of 170 patients undergoing invasive intracranial EEG monitoring. There was no significant difference in frequency of agitation among the three groups of invasive EEG monitoring. Potential risk factors identified in this group included presence of Axis II diagnosis, older age and postictal confusion or psychosis

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PSYCHOPATHOLOGY AND FAMILY DYNAMICS IN PATIENTS WITH PSYCHOGENIC NON-EPILEPTIC SPELLS (PNES)

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Rationale: Psychogenic nonepileptic spells (PNES) are seen in 10 to 40% of patients referred to epilepsy centers for seizures. The psychopathologic mechanisms that mediate PNES and the predictors of outcome are not fully understood.

Methods: Patients in the epilepsy clinics suspected to have PNES were given two standardized questionnaires, the SCL-90-R and Self-Report Family Inventory (SFI) in a prospective study. The SCL-90-R has nine syndrome scales: somatization, obsessive compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism. The SFI evaluates family relationships and has five scales: expressiveness, conflict, cohesion, health/competence, and leadership. The purpose of the study is to evaluate the findings in relationship to eventual outcome. We present preliminary results in the first 67 patients. Statistical analyses included the Wilcoxon Rank-Sum test and linear regression modeling.

Results: There were 67 patients enrolled, 49 females and 18 males with a mean age of 44.5 yrs (SD 11.8). Thirty six patients (53.7%) had high school education, while 29 patients (43.3%) had college education. The mean age of onset of spells was 37.2 yrs. (SD 14.9). Twenty one patients (31.3%) reported history of sexual abuse while 15 patients reported history of physical abuse.

SCL-90-R showed highest mean score in depression (22.5, SD 13.3), followed by somatization (21.5, SD 10.9) and obsessive compulsive symptoms (19.8, SD 9.8). Patients with history of sexual abuse had significantly high scores on somatization, obsessive compulsive symptoms, interpersonal sensitivity, depression, anxiety and hostility domains. Older patients had higher scores on somatization, obsessive compulsive symptoms, interpersonal sensitivity and depression domains.

The SFI revealed significantly higher scores in competence (mean 43.7, SD 17.4) and conflict (26.3, SD 11.7) domains. Married patients had significantly higher scores in conflict, leadership and expressiveness domains compared to divorced patients.

Conclusions: Patients with history of sexual abuse have strong psychopathology predisposing them to have PNES. Patients with PNES have higher depression and somatization scores and view their families as dysfunctional. Married patients with PNES had significant dysfunctional family interaction compared to divorced patients.

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BODY OUTLINE TASK IN EPILEPSY AND ITS MIMICKERS

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Rationale: Artwork by patients with known psychogenic non-epileptic seizures (PNES) has been found to have a significantly greater use of colors to depict their seizure experiences on a body outline compared to patients with epileptic seizures. Our previous research "A blinded pilot study of artwork in a comprehensive epilepsy center population" (Epilepsy Behav. 2005 Mar;6(2):196-202.) has indicated an increasing positive predictive value for PNES; 80% positive prediction if 10 colors of the 12 available were used. If these artistic traits are specific to PNES patients, it may become a simple but useful tool to help identify patients with a likelihood of having psychological events. Our primary objectives are: 1) to confirm the relationship between the number of colors used and PNES diagnosis, 2) observe the positive predictive value at higher number of colors used, and 3) to validate our body outline art as a unique clinical aid in the diagnosis of neurological versus psychogenic non-epileptic seizures.

Methods: From March 2009 to May 2010, patients between the ages of 18 and 70 years undergoing continuous video-EEG monitoring at St. Charles Hospital (Port Jefferson, NY) were invited to participate. The subjects were given a standard box of 24 colored pencils, a blank sheet of paper with a sex appropriate front- and back-view body outline, and directions to "express how your seizures make you feel". The subject's diagnosis was acquired after completion of the study. Logistic regression was used in prediction of the number of colors the patients used in their drawings to have PNES.

Results: Currently, 31 subjects have completed this study. There were 5 cases of PNES, 15 cases of epileptic seizures, 6 non-psychogenic non-epileptic events, 5 inconclusive diagnoses, and 1 pending diagnosis. Epilepsy diagnoses included: partial onset seizures (3), complex partial seizures with temporal focus (9), and generalized seizures (3). One subject presented with both PNES and complex partial seizures, and was included in both PNES and epilepsy groups. Subjects with non-psychogenic non-epileptic events (including sleep myoclonus, hypoglycemia, and one time seizure), inconclusive or pending diagnoses were not included in our analysis at this time. Preliminary results based on the current population (n = 20) indicated that no statistical significance has been attained between the number of colors used and PNES diagnosis (P = 0.366; odds ratio = 1.17).

Conclusions: Preliminary results show no significant difference between the PNES and epilepsy groups. These findings differ from our previous similar study. This may be due to a smaller sample size or from a difference in patient population. A stronger conclusion is expected with the enrollment of more subjects.

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CAN MULTIPLE DRUG ALLERGIES PREDICT THE FINAL DIAGNOSIS IN PATIENTS UNDERGOING VIDEO-EEG MONITORING?

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Rationale: To determine if there is an association between an increased number of medication allergies and psychogenic non-epileptic attacks (PNEA).

Methods: We retrospectively reviewed the charts of all adult patients (older than 18 years) admitted to the long-term VEM unit at Tampa General Hospital (TGH) in Tampa, FL from January 1st 2009 to December 31st 2009. All the VEM were interpreted by an attending epileptologist prior to inclusion for the study. We recorded the number of medication allergies documented on the chart along with the final diagnosis upon the completion of VEM recording. Patients with concurrent diagnosis of PNEA and ES were excluded. We divided the patients arbitrarily into three groups: A) patients with 2 or 3 drug allergies B) patients with 4 or 5 drug allergies C) patients with 6 or more drug allergies.

Results: Eighty-three patients met the inclusion criteria. Forty-seven patients fell into group A, 49% (n=23) of whom were conclusively diagnosed with PNEA. Nine patients (19%) in group A were diagnosed with ES. Fifteen patients (32%) had a non-diagnostic study. Twenty-five patients fell into group B, 68% (n=17) of whom were diagnosed with PNEA on VEM. Five patients (20%) in group B were diagnosed with ES. Three patients (12%) had a non-diagnostic study. Lastly, eleven patients fell into group C, 82% of whom (n=9) were diagnosed with PNEA, and the remaining 18% (n=2) were diagnosed with ES. Eight patients were excluded owing to concurrent diagnosis of ES and PNEA on VEM. The p-values revealed the results were not statistically significant.

Conclusions: Increased number of documented allergies appears to be an independent predictor of PNEA. We observed a clear trend of increasing likelihood of diagnosis of PNEA when the number of drug allergies increased. This information can be used to screen patients for admission to the VEM unit. Patients with 4 or more allergies can undergo an outpatient VEM with activation in hopes of obtaining the correct diagnosis, before proceeding to inpatient VEM.

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PSYCHOGENIC NON-EPILEPTIC SEIZURES (PNES): PSYCHIATRIC TREATMENT OF 12 PATIENTS

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Rationale: Psychogenic non-epileptic seizures (PNES) are events that resemble epileptic seizures (ES) but without epileptiform activity. While continuous video-EEG monitoring allows correct diagnosis of PNES, remission of PNES is low. As the outcome of PNES varies according to the therapeutic approach, this study evaluated the outcome of a small cohort of patients who were referred to a psychiatrist for evaluation and management of PNES and psychiatric comorbidities at the time of their diagnosis.

Methods: This retrospective cohort analysis included 12 patients evaluated for spell characterization at the South Texas Comprehensive Epilepsy Center (STCEC), between 2008 and 2010. The study was approved by the University of Texas Health Science Center IRB office. All the patients underwent continuous video EEG monitoring and were diagnosed as having PNES, three of them also had epileptic seizures. Demographic variables were evaluated such as age, gender, marital status, education level, employment, while clinical variables included age at onset and duration until diagnosis of PNES, associated diagnoses of epilepsy or psychiatric disorders, and use of psychotropic medications. All of the patients included in this study received psychiatric evaluation and treatment at the time of their diagnosis.The patients were followed for 6 months, they were seen in a monthly basis

Results: Most of the patients were females (83%) who received at least high school level education. Three (25%) of the patients also had ES related to head trauma. All of the patients having ES as well as PNES had a history of abuse as adults.

The most frequent psychiatric diagnoses were generalized anxiety disorder followed by depression. At 6 months follow up, six (50%) patients reported cessation of PNES, four (33%) reported a decrease in the frequency and intensity of PNES, and one reported an increased of PNES. 92% of the patients were taking SSRIs. One patient did not continue treament.

Conclusions: In this cohort we found that PNES resolved or were reduced in 83% of patients in 6 months follow up. This can be explained by prompt diagnosis and initiation of pharmacological treatment. It appears that adequate management of Generalized Anxiety Disorder produced a good outcome of PNES, while borderline personality disorder appears to carry a bad prognosis.

Demographic Data

IMAGE: tables/906035_T1.jpg

Clinical Data

IMAGE: tables/906035_T2.jpg

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WHICH SCREENING TOOLS FOR DEPRESSION IN EPILEPSY: A COMPARISON OF CONVENTIONAL AND VISUAL-ANALOGUE METHODS

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Rationale: Depression is an frequent comorbidity in patient with epilepsy (PwE) with evidence to suggest it is underdiagnosed in this patient group. Screening tools have shown to increase the dettection rate. Yet few studies have compared potentially suitable screening tools head-to-head.

Methods: We enrolled 266 consecutive attendees with a confirmed diagnosis of epilepsy at a specialised neurology service in London and compared verbal and visual analogue screening tools. This included two generic depression scales (HADS, BDI-II), one custom scale (NDDI-E) and one innovative visual-analogue scale (ET). We used DSM-IV criteria for major depression and ICD-10 criteria for depressive episode as the reference standards.

Results: All tools had similar overall accuracy with consistently high negative predictive value and sensitivity but more modest postitive predictive value and specificity throughout. NDDI-E performs particularly well on efficiency analysis. The accuracy of the visual analogue scale ET compared favourably with the other tools.

Conclusions: We suggest that the 6-item NDDI-E should be considered if a conventional scale is needed and that the ET be considered if visual-analogue is required although we acknowledge the difficulty in extrapolating from our data to other (sub-verbal) groups.

Follow up examination is necessary for all those who screen positive on any measures as these are not diagnostic tools.

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ANXIETY AND QUALITY OF LIFE IN PATIENTS WITH EPILEPSY AND PSYCHOGENIC NON-EPILEPTIC SEIZURES

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Rationale: Patients with either epilepsy or psychogenic non-epileptic seizures (PNES) have a poorer quality of life (QoL) than the general population (Szaflarski & Szaflarski, 2004). Furthermore, patients with PNES often have significantly worse QoL than patients with epilepsy (Testa et al., 2007). This inter-group difference has been explained in part by differences in mood states and adverse medication effects (Szaflarski et al., 2003), however the role of anxiety has yet to be investigated.

Methods: 38 patients with a confirmed diagnosis of epilepsy (n=18) or PNES (n=20) were assessed using the Short-Form-36 QoL measure, the State-Trait Anxiety Inventory, the Hamilton Depression Scale, the Neurological Disorders Depression Inventory for Epilepsy, and the Liverpool Adverse Events Profile (anti-epileptic drug toxicity). Multiple regression analysis was performed to determine the strongest predictors of QoL in each group.

Results: Mean QoL scores were lower in PNES (42.46) than in epilepsy (53.03). State and trait anxiety, depression and drug toxicity were all higher in PNES than in epilepsy. Lower QoL was significantly associated with higher depression ($p=0.023$), anxiety ($p=0.001$) and drug toxicity ($p=0.001$) in PNES. In patients with epilepsy, only drug toxicity was significant ($p=0.098$) in predicting 11% of the variance in QoL (R squared=0.109). Drug toxicity ($p=0.024$) and depression ($p<0.001$), but not anxiety, were significant in explaining 58% of the variance in QoL for patients with PNES (R squared=0.576).

Conclusions: Increased anxiety is associated with a reduced QoL in patients with PNES, but not epilepsy. However, anxiety is not an independent predictor of QoL, suggesting the association between anxiety and reduced QoL may be due to factors such as drug toxicity or depression. Further research is needed to determine the best predictors and therefore the factors which can be modified to improve QoL for patients with either disorder. Greater focus on improving patients' mood and reducing drug toxicity may be the most effective way of improving QoL for these patients.

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SURREALISM AND EPILEPSY: MAX ERNST'S UNE SEMAINE DE BONTé: A GRAPHIC REPRESENTATION OF NON-EPILEPTIC SEIZURES?

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Rationale: Oftentimes works of art represent, whether willingly or not, medical conditions. Not only traditional paintings or sculptures, but other forms of art can be used to such effect. That could as well be the case of Max Ernst's surrealistic novel in collage, Une Semaine de Bonté, which has several images of characters in bizarre positions that could correspond to non-epileptic seizures.

Methods: By analyzing some of the pictures of Une Semaine de Bonté and comparing them to typical semiologic features of non-epileptic seizures, the authors propose that those images might have been a graphic representation of such events.

Results: One of the main representatives of the Surrealistic movement in the beginning of the 20th Century, Max Ernst's Une Semaine de Bonté (A Week of Kindness)is regarded by many as the first groundbreaking work of collage. The contents of the book were used to criticize the European society at the time. Mostly in the final chapter, Samedy,L'élement: Inconnu, Exemple: La Clé des Chants (Saturday, Element: Unknown, Example: The Key to Songs), one can find several female characters in bizarre positions, with out-of-phase limbs, wide-eyed, and even in opistotonus. These could well represent non-epileptic seizures.

Conclusions: Similar to what can be found in more traditional works of art, the figures of Une Semaine de Bonté might have been interpreted as graphic depticions of non-epileptic seizures.

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WHOLE-GENOME SEQUENCING IN MULTIPLEX EPILEPSY FAMILIES: AN APPROACH TO IDENTIFY RARE SUSCEPTIBILITY VARIANTS

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Rationale: Epilepsy susceptibility has a clear genetic component, but causative mutations have only been identified in a handful of genes and account for a very small number of cases. Consistent with a complex disease, epilepsy exhibits extreme locus heterogeneity, making more "traditional" approaches such as GWAS and linkage studies difficult and often unsuccessful. We hypothesize that rare, highly penetrant mutations are likely to be found in families containing multiple affected individuals, and hence whole-genome sequencing (WGS) in affected individuals from such families can be used for discovery of pathogenic variants.

Methods: To test this hypothesis we performed WGS in two affected individuals from each of 9 families containing multiple individuals with non-acquired epilepsy (average 6.2 affected per family). To reduce the number of variants shared by chance, we selected the two most distantly related affected individuals from each family. The Illumina GAIIx was used to sequence each of the 18 genomes, which were sequenced to an average coverage of ~31x. The short sequence reads were aligned to the reference genome using BWA software. Two main types of variants, single nucleotide variants and small insertion-deletions, were identified using SAMTools software. We annotated and analyzed all identified variants using Sequence Variant Analyzer, an in-house software program. Within each family, the genomes of affected

relative pairs were analyzed simultaneously to identify rare shared functional variants (i.e., nonsynonymous, protein truncating, or splice site-disrupting variants). Variants were considered to be rare if they were present at a frequency lower than the cumulative incidence of epilepsy in the general population (~3%) based on comparison to HapMap and a set of 80 whole-genome or whole-exome sequenced controls from our laboratory.

Results: No rare functional variants were present in all 18 epilepsy genomes, and no shared functional variants were found in any of 12 genes already known to play a role in Mendelian forms of epilepsy. Analysis of sharing of rare functional variants in distantly-related affected individuals reduced the set of candidate variants to a manageable number for genotyping in larger cohorts. The number of rare, shared functional variants averaged 108 (min 49, max 201) per family. Very few shared variants were found in multiple families: 17 were found in 2 families, 2 in 3 families, and 1 in 4 families. This suggests that different genetic factors are responsible for epilepsy in most of the families. This work defines a set of 974 candidate variants that can be followed up by genotyping in larger cohorts and in other members of the same families.

Conclusions: We demonstrate that WGS of distantly-related affected individuals in multiplex epilepsy families is a powerful strategy for identifying potentially pathogenic candidate variants. Analysis and additional validation, including cosegregation of candidate variants in the extended pedigrees, is on-going.

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CLINICAL PHENOTYPES, EPILEPSY AND GENETICS OF VARIOUS SUBTYPES OF POLYMICROGYRIA AND EVIDENCE FOR A NOVEL LOCUS FOR BILATERAL PERISYLVIAN POLYMICROGYRIA NARROWED TO 2P16.1-P16.3

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Rationale: Polymicrogyria (PMG) is a malformation of brain cortical development. Common clinical features range from selective impairment of cognitive functions to severe encephalopathies and intractable epilepsy. It is a clinically and etiologically heterogenous condition, due to environmental causes or various genetic disorders. The aim of this study is to report the clinical phenotypes and epilepsy of several subtypes of PMG and establish genotype-phenotype correlations.

Methods: Search of our brain malformation databases at the MNH/I and HUDERF hospitals, and inclusion of all types of PMG, except those associated with schizencephaly and confirmed congenital CMV/toxoplasmosis infections; detailed review of medical records; karyotype and FISH 22q11; CGH and/or SNP microarray of genomic DNA.

Results: We enrolled 24 patients: 11 had symmetric bilateral perisylvian polymicrogyria (BPP), 2 asymmetrical BPP, 4 unilateral right PMG, 3 unilateral left PMG, and 4 bilateral posterior PMG. A 22q11 deletion was found in one patient with a unilateral right PMG and an associated large contralateral frontal heterotopia, congenital mitral stenosis, left hemiparesis, facial dysmorphism, moderate mental retardation and intractable epilepsy. A 2p13.3-p16.3 duplication was found in a patient with symmetric BPP. He presented with neonatal global hypotonia, feeding difficulties, and delayed psychomotor development. At the age of 10 years, physical examination revealed mild facial dysmorphic signs, mental retardation, severe language delay, attention deficit helped by methylphenidate, and growth deficiency treated with growth hormone, but no epilepsy.

Conclusions: The inheritance of PMG is heterogeneous. Our observations confirm that PMG, including right-sided PMG, may be associated with deletion 22q11 (DiGeorge) syndrome and can be associated with intractable epilepsy; however, the association of a large contralateral frontal heterotopia is unusual. Altogether this suggests asymmetrical gene(s) expression between the hemispheres. Phenotypic comparison with two previously published patients harboring other types of proximal 2p duplications shows a subgroup of patients with BPP sharing a common locus narrowed to 2p16.1-p16.3, one of whom presented generalized epilepsy.

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ACTION MYOCLONUS-RENAL FAILURE SYNDROME (AMRF) IN FRENCH CANADIAN FAMILIES IS DUE TO A FOUNDER EFFECT

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Rationale: AMRF, an autosomal recessive form of progressive myoclonus epilepsy with renal failure, was initially described in three French Canadian families in 1986. Subsequently, additional families were reported in the USA, Cuba, Germany, Portugal and Australia. Disease onset is usually in the late teens or early twenties, and begins with tremor and proteinuria, progressing to action myoclonus, tonic-clonic seizures and renal failure, requiring dialysis and/or renal

transplantation. The gene for this disease was recently found to be SCARB2/Limp2, encoding a lysosomal-membrane protein. A nonsense mutation c.862C>T (Q288X) in exon 7 of SCARB2 was identified in both parents of one of the original French-Canadian patients. The aim of this study was to characterize the SCARB2 mutations in French Canadian patients with AMRF and their family members, and to determine whether these mutations can be explained by a founder effect.

Methods: The original French Canadian families were contacted and family histories updated. Additional families were also ascertained. DNA was obtained on 85 family members in 5 families, and exon 7 of the SCARB2 gene was sequenced for the Q288X mutation. The genealogies of the AMRF carriers sharing this mutation were reconstructed and analyzed using the BALSAC population register. Haplotype analysis employing highly heterozygous markers was also performed.

Results: All five original AMRF patients have died. Four new patients in two families were homozygous for the Q288X mutation. In one of the new families, both parents are second degree cousins to one of the original probands and to one another. Twenty-eight unaffected individuals in four families who were not obligate carriers were found to be heterozygous for the Q288X mutation. This included one carrier couple, who were later found to have an affected son and to be related 6 generations back. Over 20 other married-in spouses of these mutation carriers had negative sequencing of the entire SCARB2 gene. In a fifth family, the mother of one of the original patients was found to carry another SCARB2 mutation, suggesting allelic heterogeneity. Genealogies of the 4 families sharing the same mutation have been traced to the beginning of the 17th century. To date, three links have been found among the families 6 generations back, and one 9 generations back. The mean kinship coefficient was significantly higher than in control French Canadian genealogies. Haplotype analysis in the region of the SCARB2 gene resulted in a shared haplotype of over 7.2 Mb involving 6 heterozygous markers, strongly suggesting identity by descent.

Conclusions: By combining genealogical and molecular data sets, we have established that four French Canadian families who were previously not known to be related share the same SCARB2 mutation that can be explained by a founder effect. Carrier screening for the founder mutation in this population can be carried out without sequencing the entire SCARB2 gene. This has important implications for genetic counseling, prenatal and preclinical diagnosis, and prevention of this debilitating disease.

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PUTATIVE SUSCEPTIBILITY ALLELES IDENTIFIED FROM A GENOME WIDE ASSOCIATION STUDY IN EPILEPSY

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Rationale: To identify genetic influences on human epilepsy we performed a genome wide association study (GWAS) on DNA samples from unrelated patients with either idiopathic generalized (IGE) or cryptogenic focal (CFE) seizures compared to unrelated healthy controls.

Methods: The Illumina HumanHap550 Bead Chip was used to genotype over 500,000 single nucleotide polymorphisms (SNPs) across the entire genome in a cohort of cryptogenic focal patients (n=295) and healthy controls (n=2,282). A second cohort of idiopathic generalized patients (n=412) and separate controls (n=3,876) was then genotyped on the same platform. Differences between SNP minor allele frequencies were compared between patients and controls using contingency analysis. Copy number variation (CNV) was identified using the Penn CNV software program. All subjects were of European ancestry and all studies approved by the local institutional review boards at each participating site.

Results: SNP rs9572727 on Chr 13q22 near the 5' end of Dachshund 1 (DACH1) was the marker that exhibited the largest statistical difference between cases and controls: focal cohort p=0.001, OR 1.93; IGE cohort p= 3.46x10-13, OR 2.89; combined cohort p=1.71x10-14, OR 2.48. Other candidate genes include MYH11 and MMP8 for the combined cohort (p=1.3x10-9 and p=6.3x10-7 respectively) ZNF695 and VGLL3 for the focal cohort and C6orf103, ENPP2 and C7orf41 for the IGE cohort. In addition, preliminary CNV analysis identified two IGE patients that carry a 1.5 Mb deletion at 15q13.3 and two separate IGE patients that carry a 1.2 Mb deletion on 16p13.11, both CNV regions were previously associated with epilepsy.

Conclusions: Our GWAS results identify several novel candidate genes for further analysis to identify potential epilepsy susceptibility alleles. These preliminary data await replication in an independent cohort and suggest that variations in genes related to developmental biology and control of gene expression may be associated with epilepsy susceptibility. In addition, we have identified CNVs on 15q13.3 and 16p13.11 in our cohort previously reported as a susceptibility factors for epilepsy. Future work will increase the size of the current cohorts and replicate these studies in independent cohorts.

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MALIGNANT MIGRATING PARTIAL SEIZURES OF INFANCY MAY BE CAUSED BY SODIUM CHANNEL MUTATIONS

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Rationale: Malignant Migrating Partial Seizures of Infancy (MMPSI) is one of the most devastating infantile epileptic encephalopathies (EE). The cause is not known. Many of the infantile-onset EE remain without an etiological diagnosis despite patients undergoing complicated protocols including advanced imaging and metabolic testing. Mutations in *SCN1A, CDKL5, STXBP1, PCDH19* and *POLG1* genes are associated with specific EE. In particular, *SCN1A* mutations are found in the recently described syndrome of Severe Infantile Multi-Focal Epilepsy (SIMFE). MMPSI could be regarded as an earlier onset, more severe form of SIMFE; this observation led us to ask whether it could be due to mutations in *SCN1A* as well as other genes associated with a range of EE.

Methods: Fifteen unrelated children with MMPSI were recruited internationally. Detailed phenotyping was performed. Patients were screened for mutations in *SCN1A, CDKL5, STXBP1, PCDH19* genes, the three common mutations of *POLG1* and 7 patients had microarray analysis for copy number variation.

Results: One patient had a de novo *SCN1A* missense mutation R862G which affects the voltage sensor segment of *SCN1A*; the same amino acid R862 has been found mutated in Dravet syndrome (R862Q;unpublished data). A second patient had a de novo deletion spanning 11.06 Mb within the 2q24-q31.1 region that includes more than 40 genes. The deletion includes *SCN1A* as well as other sodium channel subunit genes and similar deletions have been previously reported. Screening of *CDKL5* (13/15), *STXBP1* (13/15), *PCDH19* (9/10 females), the three common European mutations of *POLG1* (11/15) and the microarray studies (6/7) were otherwise negative.

Conclusions: We report the first gene mutation found in a patient with MMPSI and a deletion encompassing the same sodium channel gene. Epilepsies associated with *SCN1A* mutations range in severity from febrile seizures to severe epileptic encephalopathies including Dravet Syndrome and Severe Infantile Multifocal Epilepsy. MMPSI is the most severe *SCN1A* associated phenotype described to date. Whilst not a common cause of MMPSI, *SCN1A* screening should be considered in patients with this devastating epileptic encephalopathy.

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THE CONTRIBUTION OF PCDH19 GENE MUTATIONS IN EPILEPSY AND MENTAL RETARDATION IN FEMALES (EFMR)

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Rationale: Epilepsy and mental retardation limited to females (EFMR) is a disorder seen in both familial and sporadic cases. Mutations in the protocadherin 19 gene (PCDH19) cause EFMR. We sought to determine the frequency of PCDH19 mutations in girls presenting with seizures before 3 years of age who also had developmental delay and/or intellectual disability.

Methods: We studied 121 unrelated female patients. We analysed the patients for PCDH19 gene variation by high resolution melt curve analysis and variants were confirmed by sequencing. Where available, we analysed the inheritance of the mutation in parents and other family members.

Results: We identified PCDH19 mutations in 2/121 unrelated females. The missense mutation L25P was found in Australian sisters. Patient 1 is an almost 15 year old adolescent whose seizures began at 8 months with clusters of ~18 convulsive seizures over a few days. They were triggered by fever every 6-8 weeks but eventually afebrile tonic and tonic-clonic seizures occurred. Status epilepticus occurred once at 4 years. Seizures were refractory but responded to clonazepam with her last seizure at 13 years. Early development was normal with regression at seizure onset. She has moderate intellectual disability, autism spectrum disorder and major behavioural problems. Her older sister has severe intellectual disability with disabling aggression and also carries the PCDH19 mutation. Both parents are unaffected and negative for the mutation, indicating parental mosaicism. Their sister with a history of febrile seizures does not have the PCDH19 mutation. Patient 2 has a German father and Thai mother and presented with a tonic-clonic seizure at 17 months with her second seizure a year later. She had relatively infrequent clusters of convulsions with fever. At 14 years, she has mild to moderate intellectual disability. Patient 2 has a frameshift mutation I208A fsX222 and family members are currently being tested for the mutation.

Conclusions: We found that approximately 1.5% of females who experience seizures in infancy with a history of intellectual disability have a mutation in the PCDH19 gene. This is the first report of parental mosaicism in EFMR, a finding that carries significant genetic counselling implications for families.

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A DISTINCTIVE SEIZURE TYPE IN PATIENTS WITH CDKL5 MUTATIONS: HYPERMOTOR-TONIC-SPASMS SEQUENCE

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Rationale: Recent recognition of the encephalopathy associated with CDKL5 (cyclin-dependent kinase-like 5) mutations has led to molecular diagnosis in affected girls. Onset is by 3 months of age with tonic seizures, evolving to an epileptic encephalopathy with spasms. Here, we report a distinctive complex seizure type which will facilitate diagnosis in patients with CDKL5 mutations.

Methods: Video-EEG monitoring and clinical details of 6 girls with abnormalities in CDKL5 (3 missense mutations, 2 truncation mutations, 1 deletion) were reviewed.

Results: Four of six patients with abnormalities of CDKL5 (2 missense mutations, 1 truncation mutation, 1 deletion) showed a characteristic unusual seizure type. Onset of the hypermotor-tonic-spasms sequence was between 3.5 and 13 months (median 7.5 months), between 1.5 and 11 months after seizures first began. This sequence continued at 4 years in 3 cases. Seizures were long (3.5-17 minutes) and started with an arousal from sleep followed by a quiet phase for 10-40 seconds in 3 patients. In all patients a hypermotor phase lasting 10-60 seconds followed and evolved to a tonic phase with bilateral upper limb abduction for 20-45 seconds. The seizure then evolved to a series of epileptic spasms with arms abducted and legs adducted in a cruciate posture, which lasted 2.5-15 minutes. Ictal EEG showed bilateral frontocentral beta activity evolving to bilateral delta activity with frontal or posterior maximum during the hypermotor phase, followed by diffuse attenuation during the tonic phase and high voltage transients at the vertex with diffuse attenuation during the spasms phase. These unusual seizures occurred during the epileptic encephalopathy. The clinical history and VEM in the second year of life did not suggest this sequence in the two remaining patients.

Conclusions: We highlight a distinctive, complex hypermotor-tonic-spasms sequence as a feature of CDKL5 epileptic encephalopathy. We have found that this unusual seizure type can be suspected from history alone leading epileptologists to consider the diagnosis. Video-EEG monitoring can confirm this characteristic and unusual seizure type.

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SCREENING FOR GLUT1 DEFICIENCY IS A DIAGNOSTIC TEST IN EARLY-ONSET ABSENCE EPILEPSY: A REPLICATION STUDY

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Rationale: We recently demonstrated that over 10% (4/32) of a cohort with Early-Onset Absence Epilepsy (EOAE) had *SLC2A1* mutations leading to GLUT1-deficiency, an autosomal dominant condition with a specific and effective therapy (ketogenic diet). In this study, we sought to replicate this finding and thereby to confirm that mutational analysis of *SLC2A1* for the treatable metabolic condition GLUT1-deficiency is a useful diagnostic test in EOAE.

Methods: EOAE was defined as epilepsy of unknown cause with predominantly absence seizures, generalised spike wave (>2.5Hz) and onset under 4 years. Those with tonic or atonic seizures were excluded. A total of 40 new cases underwent *SLC2A1* mutational analysis by direct sequencing.

Results: 10% (4/40) of our new cases with EOAE had missense mutations in *SLC2A1* resulting in GLUT1 deficiency. All changes were either affecting an evolutionary conserved amino acid (Leu159Arg, Leu169Pro, Leu215Phe) or affected both amino acid polarity and charge (Leu159Arg, Gly53GluAll patients had intellect within the normal range, although learning difficulties were present in one and another had a diagnosis of autism spectrum disorder. Seizures were refractory in 1 case.

Conclusions: This study replicates our previous finding that over 10% of EOAE is due to GLUT1-deficiency in an independent cohort. We have now identified a total of 8 EOAE cases with *SLC2A1* mutations in a total of 72 EOAE patients screened to date. Given the major treatment and genetic counselling implications, *SLC2A1* mutational analysis should be part of the routine diagnostic work-up for EOAE.

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SCN1A CHANNELOPATHY IN MALIGNANT MIGRATING PARTIAL SEIZURES IN INFANCY

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Rationale: A novel SCN1A mutation was discovered in a patient who clinically fulfilled the criteria for malignant migrating partial seizures of infancy. The full-term, female patient had seizure onset at two months, with progression of hemiclonic, apneic, and generalized tonic-clonic seizures leading to recurrent status epilepticus and fatality at nine months of age. The ictal EEG showed migratory seizure foci and evolved until ictal and interictal EEGs became indistinguishable. We further characterize this novel SCN1A mutation.

Methods: Extensive metabolic, radiologic, and electrodiagnostic studies were undertaken. Genomic DNA was isolated from blood and submitted for commercial testing. The missense mutation was identified and confirmed in brain DNA obtained at autopsy. Genomic DNA from patient brain was analyzed by comparative genome hybridization and the coding exons of SCN9A were amplified. Quantitation studies of the mutant transcript were performed.

Results: The heterozygous missense mutation c.C5006A was identified by sequencing genomic DNA from blood and was confirmed in brain DNA upon autopsy. The resulting amino acid substitution p.A1669E alters an evolutionarily conserved residue in an intracellular linker of domain 4 of the channel protein. The mutant transcript is found to be expressed at levels comparable to the wildtype allele in brain RNA. No variation in copy number was detected in the chromosome region 2q24 containing SCN1A or elsewhere in the genome. No mutations were detected in the linked sodium channel gene SCN9A, which has been reported to act as a modifier of SCN1A mutations.

Conclusions: More than 600 mutations of SCN1A have been reported, most of them in patients with the sporadic syndrome severe myoclonic epilepsy of infancy (SMEI), also known as Dravet syndrome. Mutations have also been reported in patients with the related variant syndrome, SME-Borderland (SMEB), and in the milder, inherited epilepsy syndrome known as GEFS+, or generalized epilepsy with febrile seizures plus other seizure types. This report expands the spectrum of SCN1A epileptic encephalopathies to include malignant migrating partial seizures of infancy.

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MYOCLONIC EPILEPSY AS A MAJOR SYMPTOM OF A NOVEL MUTATION IN THE MITOCHONDRIAL TRNAILEU GENE

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Rationale: Myoclonic epilepsy is a major symptom in patients with mitochondrial encephalopathy. Mutations were found in the mitochondrial DNA such as tRNALys in case of MERRF (myoclonic epilepsy with ragged red fibers) or in tRNALeu in MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like epilepsodes). In both syndromes mutations were also found in tRNAPhe.

Methods: Here we describe a 40 year old patient with prominent myoclonic seizures since one year and sequencing of the mitochondrial DNA from a skeletal muscle biopsy.

Results: The myoclonia are observed at upper and lower extremities, sometimes rhythmic but independent from awakening time. Neurological examination was normal but a slight mental retardation was found in a neuropsychological testing. The patient suffered also from a progressive severe hearing loss based on a defect of the inner ear on both sides. Ictal electroencephalography (EEG) showed bilateral occipital and generalized spikes and polyspikes. The seizures and epileptic discharges could be elicited by photostimulation. The background EEG was normal. Seizures responded well to levetiracetam and the patient became seizure-free under 2000mg/d. A cranial magnetresonancetomograhy (cMRT) detected a global atrophy of the brain and mild periventricular white matter lesions. The electromyography found no pathological changes leading to a myopathy but the muscle biopsy showed abundant ragged red fibers. Sequencing of the mitochondrial DNA from the skeletal muscle biopsy revealed a novel heteroplasmic mutation (A4279G) in the mitochondrial tRNAIleu (MT-TI) gene.

Conclusions: The identified mutation changes a highly conserved nucleotide in the D-loop of this particular tRNA, which is likely to alter the tertiary structure of the tRNA affecting translation of mitochondrially encoded proteins. Interestingly, the degree of heteroplasmy of this novel mitochondrial DNA mutation was 57% in skeletal muscle but only 10% in blood, pointing to the diagnostic importance of a skeletal muscle biopsy also in patients with myoclonic epilepsy.

3.300

VARYING FEBRILE SEIZURE SUSCEPTIBILITY AMONG SCN1A GEFS+ MUTANTS

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Rationale: Mutations in the gene SCN1A, which encodes the alpha subunit of the voltage gated sodium channel Nav1.1, are responsible for two main forms of idiopathic epilepsy: genetic (generalized) epilepsy with febrile seizures plus (GEFS+) and Dravet syndrome (severe myoclonic epilepsy of infancy, SMEI). Patients within GEFS+ families display a wide spectrum of seizure phenotypes, ranging from simple febrile seizures (FS) to refractory epilepsy. In addition, patients with GEFS+ often experience FS beyond the typical cut-off age of six years. To better understand how mutations in SCN1A cause GEFS+, our laboratory has generated mice in which the human SCN1A GEFS+ mutations R1648H and D1866Y were each knocked into the mouse Scn1a gene. Heterozygous mutants from both lines exhibit reduced thresholds to the flurothyl-induced seizures and show spontaneous seizure activity. Dissociated cortical neurons from the R1648H mutants showed reduced interneuron excitability, which was consistent with observations from mouse models of Dravet syndrome.

Methods: To investigate whether genotype-phenotype correlations exist in susceptibility to FS, we compared the response of both Scn1a mutants to hyperthermia-induced seizures. Mice at ages P14-15, P22-25 and P32-35 were subjected to regulated heat from an infrared lamp with simultaneous EEG recordings. Mice were first held at 37.50C for 30 min and then their temperatures were increased by 0.50C every 2 minutes until a seizure was observed or 42.50C was reached.

Results: Under these conditions, seizures were never observed in the age-matched wildtype littermates; however, FS were observed in mice with both mutations with the lowest incidence of FS seen in the P14-15 age group. No differences were observed in the latency to the FS or the temperature at which the FS occurred between heterozygous mutants at the different age groups. However, FS in homozygous mutants occurred at lower temperatures and were more severe. Significantly fewer D1866Y mutants had FS when compared the R1648H mutants at the three time points.

Conclusions: These results demonstrate that the variability in the incidence of FS observed between GEFS+ families is due, in part, to the effect of the mutation on channel function.

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NEXT-GENERATION SEQUENCING OF REFRACTORY JUVENILE MYCLONIC EPILEPSY PATIENTS

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Rationale: Juvenile myoclonic epilepsy (JME) is one of the most common epilepsy syndromes. While most patients respond well to antiepileptic medications, a minority of JME patients continue to have seizures despite treatment. Family history is a strong predictor of JME risk, yet few genetic variants have been indentified that clearly confer disease susceptibility. Deciphering the genetic underpinnings of this syndrome could greatly improve our understanding of the pathophysiologic processes governing this and other epilepsy disorders.

Methods: In this study we sought to identify genetic variants that increase JME susceptibility using next-generation sequencing technology. Patients were selected for study if they had a diagnosis of JME and seizures that failed to be controlled with valproic acid, as determined by the treating physician. Agilent's SureSelect Human All Exon technology was used to capture the DNA regions that encode proteins from 50 refractory JME patients meeting the selection criteria. The captured fragments from each individual were then sequenced on one lane of an Illumina GAII sequencer. Sequenced fragments were aligned to the reference genome using BWA software. Single nucleotide variants (SNVs) and small insertion-deletions (indels) were called from the sequence data using SAMTools software. Annotation and statistical analyses were performed with SequenceVariantAnalyzer software. To ascertain the likelihood of variants causing JME, candidate variants

observed in JME patients and infrequently observed in 100 exome or whole-genome sequenced controls not enriched for seizure phenotypes, were genotyped in 200 non-refractory JME patients, in more than 2,000 neuropsychiatrically-normal controls , and also in a subset of affected and unaffected family members of exome-sequenced JME patients.

Results: Approximately 165,000 exons (~18,500 genes) were targeted with this technology and on average we successfully sequenced >93% of the bases in these exons with greater than 5-fold coverage. On average, 23,638 high-quality SNVs and 1,908 indels were identified in each sequenced JME exome. Furthermore, approximately 600 SNVs and 165 indels per JME patient are predicted to alter a protein-coding sequence and are not observed in any control sample. Targeted analysis of GABRA1 and EHFC1, Mendelian genes known to harbor genetic variants that cause JME, identified no rare, functional mutations in patients with JME. One rare heterozygous variant was observed in GABRA1 in one JME patient, however it is not predicted to have an effect on the coding sequence of the protein.

Conclusions: We conclude that variants in Mendelian epilepsy genes cannot explain the majority of refractory JME cases studied here. Consistent with a model of locus heterogeneity in JME genetic susceptibility, we found no single rare functional variant that accounted for all or many of the studied cases. We continue to explore the possibility that rare variants increase the risk of refractory JME.

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DOMAIN-DEPENDENT CLUSTERING AND PHENOTYPE ASSOCIATION OF LGI1 GENE MUTATIONS IN AUTOSOMAL DOMINANT PARTIAL EPILEPSY WITH AUDITORY FEATURES (ADPEAF)

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Rationale: The leucine-rich, glioma inactivated 1 gene (LGI1) encodes a secretory protein with two major functional domains: the N-terminal leucine-rich repeats (LRR) and the C-terminal epitempin repeats (EPTP). Mutations in LGI1 cause autosomal dominant partial epilepsy with auditory symptoms (ADPEAF)

(OMIM600512), a focal epilepsy syndrome with auditory symptoms as prominent ictal manifestations, with an estimated penetrance of 67%. We conducted a systematic study to investigate genotype-phenotype correlation in ADPEAF with two hypotheses: 1) the distribution of ADPEAF-causing mutations is not uniform within the LGI1 gene, and 2) phenotypic features in affected individuals differ depending on the coding domain in which mutations are found.

Methods: Clustering of mutations within the gene was analyzed for all 30 previously reported ADPEAF-causing mutations using a sliding window approach. Phenotypic and genetic information were analyzed on 52 patients with idiopathic focal unprovoked seizures from 11 ADPEAF families with LGI1 mutations. Bivariate analysis was performed using general estimating equations to test for association between mutation site and auditory symptoms. 95% confidence intervals (CI) for the odds ratios (OR) were calculated by the logit method.

Results: ADPEAF-causing mutations clustered significantly in the LRR domain (exons 3-5) of LGI1 (p =0.001). The coding domain in which mutations were located was not associated with disease penetrance. Auditory symptoms were present in 91% of patients with mutations in the LRR domain and 73% of patients with mutations in the EPTP domain (OR=3.7; 95% CI=1.1-12.5, p =0.038).

Conclusions: ADPEAF-causing mutations cluster significantly within the LRR region of the LGI1 gene, and mutations in this region are also associated with an increased likelihood of manifesting auditory symptoms in ADPEAF.

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OUTCOMES FROM THE DISCOVERY OF A NOVEL GABAA RECEPTOR MUTATION IN AN EPILEPSY FAMILY

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Rationale: WERN, a co-operation of patients, clinicians and scientists, facilitated the study; The genetic basis of familial epilepsy in Wales, which provided a platform for novel gene-discovery and candidate gene analysis, and also has generated a translational multidisciplinary communication network which facilitates the dissemination of appropriate and accurate genetic outcomes from epilepsy research.

We previously described a novel GABAA receptor subunit mutation, R97X in the gene encoding the ã2subunit of the GABAA receptor (GABRG2) in a family with a borderline GEFS+ phenotype. The mutation found to segregate with febrile seizures was not detected in 190 healthy controls. Structural modelling suggested the mutant polypeptide may traffick to the endoplasmic reticulum (ER), accumulate and be degraded. We set out to confirm this model using functional cell biology to best inform clinicians when counselling and providing information to the nuclear family harbouring the mutation.

Methods: Polymerase chain reaction (PCR) was used to amplify GABRG2 coding regions; followed by DNA sequencing reactions we performed GABRG2 and SCN1A mutational analysis on the nuclear family. Following mutation discovery, GABAA receptor subunits were cloned and PCR directed mutagenesis performed. A neuronal phenotype cell line was cultured and magnetofected with GABRá1, GABRâ2, and GABRã2 wild type(WT) or mutant receptor subunits. Surface and intracellular distribution of mutant and WT receptors were determined by co-labelling with anti-GABRã2 and anti-GABRâ2,3 subunit antibodies and confocal analysis. Following cellular outcomes the mutation was confirmed in a diagnostic laboratory prior to communicating the result to the referring clinician and the affected family.

Results: GABRG2 R97X introduces a premature stop codon, substitutes a highly conserved arginine and truncates GABRG2 with loss of all four transmembrane domains. WT GABRã2 immunoreactivity had a smooth distribution with clusters mainly detected on the cell surface and colocalised with GABRâ2 immunoreactivity. Expression of GABRã2 R97X containing receptors resulted in less cell surface cluster immunoreactivity and more diffuse intracellular labelling. GABRã2 R97X immunoreactivity also clumped intracellularly around the nucleus in close proximity to the ER; validating the structural model.

Conclusions: In this family GABAA receptor dysfunction represents a putative mechanism for GABRG2 R97X; which alters receptor composition and distribution by reducing expression and potentially compromising trafficking. Following these results, WERN collaborators including a clinical geneticist, genetic counsellor, molecular geneticist and a neurology registrar formulated a molecular report and facilitated the communication of this novel result to the original referring clinician and to the affected epilepsy family. This discovery apart from representing a molecular epilepsy outcome for the family and WERN demonstrates multidisciplinary translational research involving teams, networks and communication structures of epilepsy interested clinicians and scientists.

3.304

ESTIMATES OF FAMILIAL RISK FOR GENETIC COUNSELING IN THE EPILEPSIES

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Rationale: Previous studies of familial risk in the epilepsies have been limited by small samples size, restriction to specific epilepsy subtypes, or biased sampling schemes. Also, many studies have used family history reports from probands to identify affected relatives, which is likely to result in recall bias and underreporting. Population-based studies of adequate size with a representative sample of phenotypes are needed to eliminate selection bias and provide accurate estimates of risk that can be used for genetic counseling.

Methods: This study used data from the Genetic Epidemiology of Seizure Disorders in Rochester study (GESDR), a population-based investigation using the resources of the Rochester Epidemiology Project. The GESDR epilepsy probands comprise all 660 Rochester residents born e"1920 with incidence of epilepsy (e"2 unprovoked seizures) from 1935-1994. Occurrence of epilepsy in the first-degree relatives of these probands was ascertained by reviewing the relatives' medical records. Relatives were considered to be at risk of developing epilepsy from age at first residency in the local area until age at last residency, death, study end, or epilepsy diagnosis, whichever was earliest. Survival analysis methods were used to estimate cumulative incidence of epilepsy to age 40 in siblings and offspring of probands with epilepsy, within strata defined by the proband's epilepsy syndrome, sex, and age at epilepsy onset. We also calculated standardized incidence ratios (SIRs), using the population incidence rates from Rochester, MN as the reference.

Results: The risk of epilepsy to age 40 in the general population of Rochester, MN was 1.4%. Risks were increased in relatives of probands with epilepsy (siblings 4.6%, offspring 3.9%), and the magnitude of increased risk varied according to proband epilepsy type, proband sex, and relative type. The greatest increases in risk were for relatives of probands with idiopathic generalized epilepsies (siblings 8.2%, offspring 8.2%). Among relatives of probands with focal epilepsy of unknown cause, risks were significantly increased in offspring (risk=3.5%, SIR=3.5) but not in siblings (risk=1.0%, SIR=1.1). Among the relatives of probands with focal epilepsy of structural/metabolic cause, risks were comparable to population rates (siblings 1.9%, offspring 2.4%). Risks in siblings were significantly increased in the families of both female (5.8%) and male probands (3.5%). However, risks in offspring were increased only in the families of female probands (5.3%) and not in the families of male probands (1.9%).

Conclusions: The GESDR study addresses the shortcomings of previous studies by using a population-based design and rigorous data collection methodology. These data provide accurate estimates of familial risk that can inform epilepsy research and genetic counseling.

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METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) DEFICIENCY AND INFANTILE EPILEPSY

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Rationale: A rare recessively inherited defect leading to deficiency of the enzyme 5, 10-methylenetetrahydrofolate reductase (MTHFR) underlies one form of hyperhomocysteinemia. We describe the association of severe MTHFR deficiency and neurological manifestations with particular attention to neurodevelopment and evolution of epileptic seizures.

Methods: Longitudinal Case Study over 10 years and literature review

Results: A 9 year old female infant born to Caucasian non-consanguineous parents presented with infantile spasms and developmental regression in the first year. The biochemical profile of low plasma methionine (undetectable), and high homocysteine (117 μmoles/gm creatinine) suggested hyperhomocysteinemia. Enzyme assay in skin fibroblasts confirmed severe MTHFR deficiency (patient 0.92, control 13.3+/-4.6 nmole/mg/hr). Molecular genetic studies identified compound heterozygosity for 2 variant polymorphisms (c.677C>T, and c. 1298A>C) and a splicing mutation (c.1348+1G>A). This is a novel mutation that removes a splice site at the end of exon 7 resulting in a premature stop codon that truncates the protein losing exons 8-11. CSF neurotransmitter analysis showed extremely low level of 5-methyl tetrahydrofolate of <5 (40-128 nmol/L).The course of epilepsy has been characterized by progression to severe epileptic encephalopathy. Periventricular white matter change consistent with demyelination is seen on MR imaging. Treatment protocols include; oral betaine, supplementation with methionine, folic acid, and 5-methyltetrahydrofolate with questionable benefit. Epileptic seizures remain pharmacoresistant to antiepileptic medications singly and in combinations. Frequent bouts of status epilepticus have led to multiple hospitalizations, and neurosurgical interventions (corpus callosotomy, vagal nerve stimulation).

Conclusions: Severe MTHFR deficiency is an important diagnostic consideration in infantile epileptic encephalopathies. Early diagnosis and specific treatment interventions are possible. Further research is needed into effective treatment of epilepsy and prevention of complications in this disorder. Genotype phenotype correlations will be explored in the light of available biochemical and molecular genetic data

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ASSOCIATION STUDY SHOWS RELATIONSHIP BETWEEN MESIAL TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS AND *IL1B* AND *PTPRM* GENES

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Rationale: Mesial temporal lobe epilepsy (MTLE) is one of the most common and intractable forms of epilepsy showing a complex mode of inheritance. Previous studies have associated polymorphisms in pro-inflammatory cytokine interleukin 1-beta (*IL1B*) gene and increased predisposition to MTLE associated; however these findings are still controversial. In addition, we have found that the protein tyrosine phosphatase, receptor type, M gene (*PTPRM*) is up-regulated in brain tissue from patients with MTLE. *PTPRM* gene product regulates a variety of cellular processes including cell growth, differentiation and mitotic cycle. The aim of this study was to investigate if *IL1B* and *PTPRM* genes are associated with the phenotype in mesial temporal lobe epilepsy (MTLE).

Methods: DNA samples were obtained from 203 unrelated patients with MTLE, as well as 204 unrelated controls, with no history of epilepsy. We selected five SNPs within *IL1B* and 110 SNPs within *PTPRM* from HapMap database. SNPs were genotyped using the SNPlexTM genotyping system (Applied Biosystems). Minor allele frequency (MAF>0.05), linkage disequilibrium (r^2^>0.8) and Hardy-Weinberg equilibrium (HWE pvalue>0.05) were estimated using the HAPLOVIEW software. Statistical analysis was performed by a logistic regression model with Bonferroni correction for multiple comparisons.

Results: We found association between SNP rs3730364 in the *IL1B* gene and MTLE [p=1.4x10^(-14), OR=0.11; 95%CI: 0.06 - 0.21]. Furthermore, we found 11 SNPs in with *PTPRM* gene which were significantly associated with MTLE (rs727037, rs638251, rs671369, rs1443616, rs1016188, rs583909, rs565798, rs9807775, rs8087904, rs3786368, rs727027 and rs634438) [p=1.2x10^(-11), OR= 0.12; 95%CI: 0.07-0.24 for rs727027].

Conclusions: Our association study shows that there is a relationship between one SNP in the *IL1B* gene as well as several SNPs in the *PTPRM* gene and MTLE. However, none of these SNPs appear to be functional variants. Although much progress has been made in the characterization of genes for the monogenic and rare forms of epilepsy the common epilepsy syndromes, usually showing complex inheritance remain a major challenge for gene identification, our study hopes to shed some light into this area.

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3.307

RESPONSE TO ANTIEPILEPTIC DRUGS IN MESIAL TEMPORAL LOBE EPILEPSY IS A POLYGENIC TRAIT

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Rationale: Mesial temporal lobe epilepsy (MTLE) is associated with a significant proportion of patients who do not respond to treatment with antiepileptic drugs (AEDs). One hypothesis to explain individual differences in drug response is the presence of allelic variations in candidate genes which could be responsible for degreased efficacy of antiepileptic drugs. The purpose of this study was to investigate whether single nucleotide polymorphisms (SNPs) on drug-transporter and drug-metabolism genes could be associated with pharmacoresistance in a large group of patients with MTLE.

Methods: : We genotyped 44 dbSNPs within 4 different drug-transporter genes (RALBP1, ABCB1, ABCC2, ABCC4) and 95 dbSNPs within 9 drug-metabolism genes (CYP1A1, CYP1A2, CYP1B1, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5). We ascertained 164 drug-resistant and 78 drug-responsive patients, who were seizure free on AEDs. The significance of allelic and genotypic association was assessed using logistic regression (logistf function in R environment). P-values were corrected by Bonferroni. As a genomic control we genotyped an additional 119 SNPs. Fst and AMOVA (Arlequin v.3.11) were performed in order to analyze the genetic structure of both groups. In addition, we quantified the expression of ABCC2 transcripts (using Real-Time PCR, ABI7500, TaqMan system™) in hippocampal tissue collected during epilepsy surgery in 11 patients with refractory MTLE.

Results: We found a significant association for allele rs3740066C (Ile1324Ile) in the ABCC2 gene, which was more frequent in the pharmacoresistant group (p=0.04). In addition, we found that expression of ABCC2 was higher in patients with refractory MTLE when compared to autopsy controls (ANOVA, p=0.0170). In addition, we found significant associations with 4 intronic SNPs in 3 drug metabolism genes: CYP1B1: rs2551188TT (p=0.02); CYP2C9: rs4086116CT (p=0.005) and rs2153628AA (p=0.02), and CYP1A2: rs12904742GG (p=0.005). We calculated that the overall contribution of the 4 associated genes to phenotype of pharmacoresistance was around 10%.

Conclusions: We found evidence that multiple genetic factors are involved in determining pharmacoresistance in patients with MTLE, thus confirming the polygenic nature of the trait.

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GENES ACTING IN GROWTH, DIFFERENTIATION, AND NEURONAL MIGRATION POTENTIALLY INVOLVED IN TEMPORAL LOBE EPILEPSY

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Rationale: The Temporal Lobe Epilepsy (TLE) caused by mesial sclerosis is probably a multifactorial disease influenced by genetic and environmental factors. The aim of this study is to evaluate genes potentially associated with susceptibility to the development of TLE through the search for DNA polymorphisms in promoter and coding regions of genes potentially involved in the etiology of TLE. The called “susceptibility genes” contributes a small effect that, individually, is not sufficient or necessary to determine the disease phenotype. Have been described more than 60 association studies in TLE involving over 30 different genes, however, still remain uncertainties in the associations and failures in replication.

Methods: By the time we selected 50 patients with TLE and 50 controls without personal and family history of neurological and psychiatric diseases. The search for new polymorphisms is initially done in silico and, once validated, is experimentally investigated by direct sequencing of DNA.

Results: Initially we selected 115 genes involved in different biochemical pathways that lead to hyper or hypo-neuronal excitation, of ion channels function or their subunits, neurogenesis, metabolism, plasticity and neuronal migration. We have studied 39 polymorphisms in 26 genes, of which 16 SNPs were validated experimentally on 12 different genes (TMEM1, EFHC1, ME2, BRD2, BDNF, CHRNA2, RTN4, SCN1A, CLCN2, JRK, RELN, KCNQ2). The NRG1 gene, has shown potential association with pathology. The 'T' allele (rs35641374 [C/T]) seems to have a significant protective role (controls = 15.3%, patients = 4,2%). The PLXNA2 gene (SNP rs2782948, [C/T]) also showed association with TLE, where again the polymorphic allele seems to have a protective role (controls = 38%, patients = 30%; P 0,001).

Conclusions: Polymorphisms in the NRG1 gene (Neuregulin 1), involved in neuronal growth and differentiation, and PLXNA2 (plexin A2), active in axon guidance during nervous system development, have shown allele frequencies different when comparing patients and respective controls, indicating a role potential in the development of TLE. The number of polymorphisms in these genes and the number of patients investigated should be increased in order to evaluate which one (s) possible (s) haplotype (s) would be associated with TLE, in addition to the replication of results. The purpose of this study was to broaden the knowledge about the molecular events that predispose to TLE. With the molecular characterization of TLE we intend to contribute to a better understanding of the complex pathways that characterize the neuronal hyper-excitability.

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MUTATION SCREENING OF *GRIN2A* AS A CANDIDATE GENE FOR IDIOPATHIC FOCAL EPILEPSIES

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Rationale: Idiopathic focal epilepsies comprise various epilepsy syndromes characterized by the unifying EEG trait of centrotemporal spikes (CTS). Deletions of the chromosomal region 16p13.2 including *GRIN2A* were previously identified in three patients with complex phenotypes of focal epilepsies with CTS, dysmorphic features and various degrees of intellectual disability (Reutlinger et al., Epilepsia, in press). *GRIN2A*, coding for the alpha 2 subunit of the glutamatergic NMDA receptor is involved in the modulation of synaptic activity, representing a prime candidate gene for epileptogenesis.

Methods: Mutation analysis of *GRIN2A* including all exons, exon-intron boundaries and the promoter region was performed in a cohort of 44 patients with CTS (Benign Rolandic Epilepsy n=35, Atypical Benign Partial Epilepsy n=9) using the NCBI Primer Set RSS000057426.1 and additionally designed primers. NovoSNP was used for the evaluation of single nucleotid polymorphisms (SNPs) and indels. Pathogenic implications of identified coding variants were assessed by four different in-silico analysis programs (PolyPhen, SIFT, SNAP, Panther). For intronic SNPs, splice site analysis was performed using NetGene 2, Splice View and HSF2.4.

Results: In total, 26 single nucleotide polymorphisms were identified, including 5 previously unknown non-coding variants and 3 missense mutations resulting in amino acid exchange. A possibly pathogenic mutation (c.728C>T, p.Ala43Val) was identified in a patient with Benign Rolandic Epilepsy, behavioural problems and learning disability, which was not observed in 384 population controls.

Conclusions: Mutation analysis of *GRIN2A* in patients with CTS and epilepsy syndromes of the Rolandic spectrum identified one missense mutation localized in the ligand-binding domain of the alpha-2 NMDA receptor subunit. This further supports earlier findings suggesting the involvement of altered glutamatergic transmission in the generation of centrotemporal spikes. Further studies including larger patient cohorts and functional analysis of the mutant protein are needed to validate these findings.

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EVALUATING THE CLINICAL USE OF GENETIC TESTING IN PATIENTS WITH DRAVET AND DOOSE SYNDROMES

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Rationale: Mutations in the neuronal voltage-gated sodium channel á1-subunit gene (*SCN1A*) have been identified in many patients with phenotypes within the generalized epilepsy with febrile seizures plus (GEFS+) spectrum. In addition, the International League Against Epilepsy Genetics Commission indicates that genetic testing for *SCN1A* mutations is one of most clinically useful among the tests for genes that influence risk for developing epilepsy (Ottman et al. 2010). The aim of this study is to search for mutations in the *SCN1A* gene in patients with severe myoclonic epilepsy of infancy (SMEI or Dravet syndrome) and myoclonic astatic epilepsy (MAE or Doose syndrome), both within the GEFS+ spectrum, and to establish genotype-phenotype correlations.

Methods: We performed mutation screening in the *SCN1A* gene in nine patients with SMEI and 12 with MAE. Prediction algorithms were used to analyze the possible impact of the amino-acid changes in the protein function. In addition, multiplex ligation-dependent probe amplification (MLPA) is being used to detect copy number variations within *SCN1A*.

Results: Mutation analysis revealed six potentially deleterious variants only in patients with SMEI: three missense mutations (c.829T>C, c.971A>C and c.5434T>C) that lead to amino-acid residue substitutions and are predicted to affect protein function, an insertion (c.3719_3720insGATA) that promotes a frameshift and two splice donor site mutations (IVS4+1G>A and IVS8+3G>T). To date, preliminary MLPA analysis shows no abnormalities.

Conclusions: Since potentially deleterious variants were found only in patients with the most severe phenotype, our results indicate that molecular testing for clinical purposes seems to yield best results in patients with SMEI. According to our results, the main clinical feature associated with deleterious mutations in *SCN1A* was the occurrence of seizures with low fever (37.5-38°C), which was present in all patients with *SCN1A* mutations in our study.

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PHENOTYPE DEFINITION IN LGI1-RELATED EPILEPSY

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Rationale: Autosomal dominant partial epilepsy with auditory features (ADPEAF) is an idiopathic focal epilepsy syndrome with auditory symptoms or receptive aphasia (ASRA) as prominent ictal manifestations. These symptoms suggest localization of the epileptogenic zone to the lateral temporal lobe; hence the syndrome has also been called autosomal dominant lateral temporal lobe epilepsy (ADLTE). The occurrence of ASRA in e”2 affected family members has been used as a simple definition of ADPEAF, and mutations in the leucine-rich, glioma inactivated 1 (LGI1) gene have been found in up to 50% of families meeting this definition. Refinement of the syndrome definition is important to improve identification of families likely to carry LGI1 mutations and facilitate selection of families for identification of new ADPEAF susceptibility genes.

Methods: We used an epidemiologic approach to refine syndrome definition in ADPEAF by comparing focal seizure symptoms in ADPEAF families with and without LGI1 mutations. To distinguish ADPEAF from other forms of familial temporal lobe epilepsy, we focused on symptoms characteristic of mesial temporal lobe (MTL) seizure onset: visceral/epigastric sensations, fear, déjà-vu, olfactory auras, and oral and limb automatisms. The study population comprised 112 subjects with idiopathic focal epilepsy from 30 families containing e”2 individuals with ASRA, 11 of which had LGI1 mutations. We compared occurrence of MTL symptoms in families with and without mutations, first in all individuals with focal epilepsy and then in individuals with ASRA specifically (N=89). We used generalized estimating equations to account for within-family correlations.

Results: The two sets of families were similar with respect to sex, ethnicity, education, age at onset, and number of individuals with ASRA. Among all individuals with focal epilepsy, the proportion of individuals with MTL symptoms did not differ between families with and without mutations. Among individuals with ASRA, however, the proportion with MTL symptoms was lower in families with LGI1 mutations than in those without (29% vs. 55%, p=0.049). This difference was attributed to a lower proportion with visceral/epigastric symptoms among individuals with ASRA in the mutation families vs. the non-mutation families (10% vs. 32%, p=0.017). The specific types of auditory symptoms also differed between the two groups of families: individuals with ASRA were less likely to have auditory distortions in the mutation families than in the non-mutation families (17% vs. 52%, p=0.002).

Conclusions: These findings suggest that individuals with ASRA have different symptom profiles in families with vs. without LGI1 mutations. The higher frequency of visceral/epigastric symptoms in the non-mutation families suggests that some of these families may have more MTL involvement. The occurrence of ictal auditory symptoms or receptive aphasia in e”2 affected members with focal epilepsy may be insufficient to define ADPEAF. Ruling out MTL seizure symptoms may better facilitate identification of families likely to have LGI1 mutations.

3.312

PROFOUND ICTAL APNEA IN PCDH19 RELATED EPILEPSY: 2 CASES WITH NOVEL PHENOTYPIC AND GENETIC FINDINGS

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Rationale: Epilepsy and Mental Retardation Limited to Females (EFMR) is a rare condition in which otherwise normal female infants develop sudden onset of seizures. The clinical spectrum is broad, including a Dravet-like syndrome with multiple seizure types. The disease-causing gene was recently identified as PCDH19, which resides on the X chromosome and encodes protocadherin 19. Ictal apnea (IA) has not been reported in this syndrome, and the genetic mechanism by which alteration of PCDH19 results an atypical X-linked inheritance pattern is uncertain.

Methods: Case 1: Whole genome array CGH was performed using the SignatureChip 105K oligonucleotide array (10-35 Kb spatial resolution).

Case 2: Standard targeted sequence analysis of exons 1-6 of the PCDH19 gene was performed.

Results: Case 1: An otherwise healthy 19 mo old girl presented with new onset seizures at age 11 mos. Initial seizure semiology was bilateral upper extremity clonic movements and unresponsiveness. Seizures were refractory to multiple AED trials but finally stopped with topiramate. At age 18 mos she had another seizure cluster with eye opening, upper extremity flexion, and profound apnea with desaturation to SaO2 of 10%. Ictal EEG revealed biposterior onset of rhythmic sharp theta activity with rapid secondary generalization. Inter-ictal EEG was normal. Brain MRI was normal. Family history was negative. CGH microarray detected a deletion in Xq21.33-Xq22.1 (estimated size 2.89-3.01 Mb), which contains the PCDH19 gene.

Case 2: An otherwise healthy 22 mo girl presented with new onset seizures at age 8 mos. Initial seizure semiology was eye opening, variable extremity movements, unresponsiveness, and apnea with desaturation to a SaO2 of 50%. Seizures were refractory to multiple AED trials but ultimately controlled on phenobarbital. At age 20 months, she had another seizure cluster with similar semiology and profound ictal apnea with desaturation to SaO2 of 6%. Ictal EEG showed biposterior onset of rhythmic sharp theta activity with rapid secondary generalization. Interictal EEG was normal. Brain MRI was normal. Family history was negative. PCDH19 sequence analysis revealed heterozygosity for c.434_435insG alteration in exon 1 of the PCDH19 gene, which has not been previously reported.

Conclusions: Our findings have two fundamental implications. First, profound IA is unusual and has not been described in the setting of a specific epilepsy syndrome outside of the neonatal period. These two cases suggest IA may be a unique seizure type in children with PCDH19 related epilepsy. Additional cases are necessary to determine the strength of this association. Second, previous authors have proposed a dominant negative model to explain the atypical X-linked inheritance pattern. Case #1 is the first affected female with a deletion of the PCDH19 gene, which represents the most compelling evidence to date that the dominant negative model is incorrect.

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ASSOCIATION OF INTRONIC VARIANTS OF THE KCNAB1 GENE WITH LATERAL TEMPORAL EPILEPSY

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Rationale: In a recent multicentre screening of common single-nucleotide polymorphisms (SNPs), intronic variants of the KCNAB1 gene were found significantly associated with focal epilepsy in a population-specific manner. KCNAB1 may be implicated in lateral temporal epilepsy (LTE) due to its functional interaction with the LGI1 gene. This study investigated association between polymorphic variants across the KCNAB1 gene and LTE.

Methods: The allele and genotype frequencies of fourteen KCNAB1 intronic SNPs were determined in 142 Italian LTE patients and 104 healthy controls and statistically evaluated.

Results: A single SNP located near the 3'end of KCNAB1 was significantly associated with LTE after multiple testing correction (odds ratio = 2.25; 95% confidence interval 1.26-4.04; P = 0.0058). Moreover, haplotype analysis revealed two haplotypes with frequencies higher in cases than in controls, one of which was significantly associated with LTE after Bonferroni correction (P = 0.0001) and the other conferred a high risk for the syndrome (odds ratio = 12.24; 95% confidence interval 1.32-113.05; P = 0.028).

Conclusions: Our results confirm association of KCNAB1 with focal epilepsy and show that this gene may confer risk for particular forms rather than the whole class of focal epilepsies.

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GENOME-WIDE LINKAGE ANALYSIS IN ADPEAF FAMILIES WITHOUT MUTATIONS IN LGI1

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Rationale: Autosomal dominant partial epilepsy with auditory features (ADPEAF) is a genetic form of temporal lobe epilepsy with auditory symptoms and receptive aphasia as prominent ictal manifestations. Mutations in the leucine rich, glioma inactivated 1 gene (LGI1) are found in up to 50% of families with ADPEAF, but the genes that influence risk in the remaining families have not yet been identified. We carried out genome-wide linkage analysis in 11 families with clinical symptoms consistent with ADPEAF and without LGI1 mutations, to identify chromosomal regions likely to harbor additional genes that raise risk for this syndrome.

Methods: Families were included if they contained e"2 individuals with focal epilepsy with ictal auditory symptoms or receptive aphasia. Initial analyses used 390 microsatellite markers spaced at an average of 9cM throughout the genome, genotyped at the Center for Inherited Disease Research. Additional microsatellite markers were later typed in a region on chromosome 1 showing elevated LOD scores. Two-point and multipoint linkage analyses were performed as implemented in GENHUNTER2, assuming autosomal dominant inheritance with age-dependent penetrance of 67%, no sporadics, and a susceptibility allele frequency of 0.001. Two definitions of affection status were used: focal non-acquired unprovoked seizures (narrow) and any form of non-acquired unprovoked seizures (broad). Individuals with unprovoked seizures associated with structural or metabolic CNS insults were classified as unknown, and those with febrile or other acute seizures were classified as unaffected.

Results: The 11 included families contained a total of 245 individuals (192 living, 53 deceased), of whom 135 were genotyped. The number of individuals per family with non-acquired epilepsy ranged from 2-7 and averaged 4.3 (focal 3.4, generalized 0.2, both 0.1, unclassifiable 0.6). Among individuals with focal epilepsy, an average of 2.7 (range 2-4) individuals per family had ictal auditory symptoms or receptive aphasia. The highest HLOD was observed for the focal epilepsy phenotype at 262cM on chromosome 1 (HLOD=2.65, alpha=0.76). HLODs were also e"1.5 in two other regions: chromosome 1, 154cM (HLOD=1.50, alpha=0.43) and chromosome 17, 121cM (HLOD=1.53, alpha=0.53). These results were strongly influenced by one large family with some clinical features atypical of ADPEAF (i.e., 3/7 individuals with epilepsy had previous febrile seizures). When this family was excluded from the analysis, the highest HLOD was on chromosome 17, 121cM (HLOD=1.82, alpha=0.63).

Conclusions: The findings indicate regions to be prioritized for additional analyses to identify susceptibility genes for ADPEAF. Collaborative studies are underway to increase the sample size and include dense SNP genotyping for further analyses.

3.315

COMMON GENETIC VARIATION IN DRUG METABOLISING ENZYMES AS A DETERMINANT OF CARBAMAZEPINE DOSE REQUIREMENT IN NEWLY DIAGNOSED EPILEPSY

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Rationale: A number of drug metabolising enzymes (DMEs), including cytochrome P450s (CYPs), uridine diphosphate-glucuronosyltransferases (UGTs) and microsomal epoxide hydrolase (EPHX1), contribute to the inactivation of carbamazepine (CBZ). Single nucleotide polymorphisms (SNPs) in genes encoding these enzymes may alter their expression or activity and could, theoretically, affect serum concentrations of CBZ and individual dose requirement. We have assessed whether genetic variation across six major DMEs involved in CBZ metabolism is associated with maintenance doses of the drug when employed as monotherapy in people with newly-diagnosed epilepsy.

Methods: A total of 161 individuals with newly diagnosed epilepsy were included in the analysis. Each had been seizure-free for at least 12 months on a stable dose of CBZ as monotherapy. A total of 91 tagging

and known functional SNPs across six DMEs (CYP1A2, CYP2C8, CYP3A4, CYP3A5, EPHX1 and UGT2B7) were genotyped on a Sequenom MassARRAY iPLEX platform. Associations between maintenance dose of CBZ, demographic variables (age, gender, epilepsy type), and genotype of individual SNPs were identified using ANOVA and linear and stepwise regression analysis, as appropriate. Haplotype analysis was also performed, using the solid spine of linkage disequilibrium method to define blocks and PHASE software (version 2.1) to infer haplotypes. Correction for multiple comparisons was performed by false discovery rate (FDR).

Results: Univariate analysis identified patient age and the genotype of seven individual SNPs as being independently associated with the maintenance dose of CBZ (all $p<0.05$; prior to correction for multiple testing). Three of these SNPs (rs4646450, CYP3A5, p=0.002; rs4149229, EPHX1, p=0.010; rs3924194, UGT2B7 p=0.014) remained significantly associated with dose after stepwise regression, with a significant overall model fit (adjusted r^2=13.2%, $p_{residual}$=0.000015). Multivariate regression modelling of haplotype blocks, with age included as a covariate, identified four haplotypes that were associated with CBZ dose. Of these, only the six-SNP block 1 haplotype (ACGCCG) remained significantly associated with dose (p=0.00025, r^2=9.7%) after stepwise regression.

Conclusions: These findings suggest that variability in genes encoding CYP3A5, EPHX1 and UGTB7 may contribute to CBZ dose requirement in people with newly diagnosed epilepsy. Haplotype analysis better explains dose variability than single SNP analysis, as it is more representative of variation across entire genes and less likely to exclude any unidentified causal variants. However, even if these data were replicated in an independent cohort, it is unlikely, given the modest size of the effect reported here, that genetic variability in DMEs accounts for a sizeable proportion of inter-individual differences in CBZ dose requirement.

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CONCORDANCE OF SEIZURE SEMIOLOGY AND PHARMACOSENSITIVITY IN SIBLING PAIRS FROM THE EPILEPSY PHENOME/GENOME PROJECT (EPGP)

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Rationale: Systematic phenotype definition in the epilepsies can help direct the search for susceptibility genes. Prior studies have identified distinct genetic effects on localization related (LRE) vs. generalized epilepsy (GE), myoclonic vs. absence seizures, and the generalized tonic-clonic seizure types within the idiopathic generalized epilepsies (IGEs). Here, we examine the genetic effects on specific seizure semiology within LREs, and on pharmacosensitivity (PS) to antiepileptic drugs (AEDs).

Methods: We examined seizure semiology and pharmacosensitivity (PS) in sibling pairs from EPGP, a multicenter collaborative consortium that collects in-depth phenotype and genotype data from a large number of patients with epilepsy to investigate the genetic influences on common and rare forms of epilepsy and pharmacosensitivity. We completed seizure symptom data on 102 sibling pairs with IGE and/or LRE. 51 of these pairs are concordant for IGE, 31 are concordant for LRE, and 20 are discordant (one sibling has IGE, the other LRE). Within the 31 pairs concordant for LRE, we examined concordance of focal seizure symptoms in the following categories: aphasia, autonomic, psychic, sensory, and motor. We also examined the concordance of PS within 20 sibling pairs in which both siblings were definitively classified according to PS. The analytic approach fit a logistic regression model in which presence of a symptom category in the proband was the predictor of presence of the same category in the sibling. Under the null hypothesis of no familial aggregation of symptom types, there should be no association between proband and sibling. The extent to which the estimated log-odds differs from zero was used to test for association.

Results: Probands and siblings were significantly associated for aphasic (1-sided p-value=0.003), autonomic (0.04), psychic (0.012), and sensory (0.004) symptom categories. The sibpair association for motor symptoms was suggestive (p=.074). The results of analysis of pharmacosensitivity data were suggestive of sibling concordance, though numbers were too small for statistical significance. Among siblings of probands who were PS (N=12), all were also PS, whereas among siblings of probands who were not PS (N=8), 6/8 were PS (p=0.15).

Conclusions: Analysis of focal seizure symptom concordance in EPGP sibling pairs provides evidence for distinct genetic effects on aphasic, autonomic, sensory, and possibly motor symptoms. This evidence can help clarify the role of genes in determining the specific manifestations of the epilepsies, and may allow a priori identification of disease subtypes that are more likely to share susceptibility genes within the focal epilepsies. Analysis of PS data in sibling pairs suggests that there may be a genetic effect on pharmacosensitivity. As enrollment and data collection proceeds in EPGP, analyses using larger numbers of subjects will better address this question, and will allow stratification of PS by epilepsy type.

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IDENTIFICATION AND CHARACTERISATION OF ENDOPHENOTYPES FOR EPILEPSY THROUGH MRI

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Rationale: The experience of the research community to date has shown that endophenotypes are required to augment the power of genetic mapping studies in complex forms of epilepsy. We are applying in-vivo quantitative magnetic resonance imaging (QMRI) to identify subtle structural variations in the brain that are both heritable and involved in the development of temporal lobe epilepsy

Methods: Our study design involves acquiring brain MRI scans on index patients with temporal lobe epilepsy together with an unaffected same gender sibling and healthy controls. MRI scans were processed using a fully automated brain reconstruction tool (FreeSurfer). We have applied numerous sets of analysis across these three groups to identify brain structures showing characteristics of good endophenotypes - heritable, associated with the disease and measureable in healthy siblings.

Results: Results to date have highlighted several structures as candidate endophenotypes including the thalamus and anterior cingulate cortex

Conclusions: The novel endophenotypes identified in this study are being measured in a larger cohort of temporal lobe epilepsy patients for whom whole genome association data is already available.

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FAMILIAL LATERAL TEMPORAL LOBE EPILEPSIES: THE CLINICAL AND GENETIC SPECTRUM IN ITALY

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Rationale: Autosomal dominant lateral temporal lobe epilepsy (ADLTE) is genetically heterogeneous, with LGI1 gene mutations accounting for less than 50% of ADLTE families. Additional ADLTE-related genes are unknown. It may be hypothesized that this genetic heterogeneity is caused by differences in the clinical or genetic characteristics of the families. Here we report the clinical and genetic spectrum of ADLTE in Italy.

Methods: In a collaborative study of the Commission for Genetics of the Italian League against Epilepsy spanning the last 8 years we selected 33 families in which at least two members showed auditory and/or aphasic seizures, suggesting a lateral temporal onset. The probands and affected family members underwent a complete clinical, EEG and MRI study. Probands' DNAs were tested for LGI1 mutations by direct sequencing. We also calculated the clinical penetrance of LGI mutations in mutated families as well as the penetrance of the disease among proband's relatives in all pedigrees.

Results: Based on genetic analysis, we subdivided the families in two main groups:

1) 9 families (38 affected subjects - 7 deceased) with LGI1 missense mutations (27 %)

2) 24 families (78 affected subjects - 14 deceased) without LGI1 mutations (73 %).

The clinical features of the patients belonging to the two groups did not differ substantially as to age at onset (20 vs 18 years), frequency of auditory auras/aphasic seizures (73% vs 77%), and occurrence of tonic-clonic seizures (61% vs 63%). Interestingly only in the second group there were additional family members (8) with idiopathic generalized epilepsy whereas febrile seizures were equally distributed in both groups (4 and 6 cases respectively). The penetrance of LGI1 mutations calculated on 6 families was 58%, which is likely underestimated due to limited DNA availability. Segregation analysis of probands' first and antecedent second degree relatives estimated a penetrance of 78% in mutated ADLTE families, whereas penetrance was 54% in families without LGI1 mutations.

Conclusions: ADLTE is caused by LGI1 mutations in about 27% of italian families, a percentage significantly lower than hitherto reported. In the non-mutated group the penetrance is significantly lower than in mutated families, suggesting that part of the families currently classified as ADLTE may in fact exhibit complex inheritance of lateral temporal epilepsy.

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RECRUITMENT OF SUBJECTS FOR GENETIC STUDIES OF TEMPORAL LOBE EPILEPSY

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Rationale: Temporal lobe epilepsy (TLE) is the most common partial epilepsy in adults and is an important target for genetic studies. Because TLE is prevalent, a large number of patients might be expected to be eligible for and participate in studies; this may not be the case. Here we describe recruitment strategies and enrollment results in a genetic study of TLE, discuss issues that may arise during recruitment, and provide suggestions for future studies.

Methods: Potentially eligible participants were ascertained from the Columbia University Comprehensive Epilepsy Center (CEC) and The Neurological Institute Department of General Neurology (NI) through chart review of incoming patients and consultation with treating physicians. Over 1,400 adult and 302 pediatric patients have been seen at the CEC, and 384 at the NI in the past two years. In addition, over this time period, more than 900 patients were seen by another NI neurologist with a large proportion of epilepsy patients and separate records. To be eligible for the study, patients had to have non-symptomatic TLE (Mesial Temporal Sclerosis and Focal Cortical Dysplasia were not excluded), good quality MRI and EEG, age of onset d" 35, and no known disease-associated mutation. Potentially eligible patients were approached by their treating physician who obtained permission for study researchers to initiate contact.

Results: 1,840 patients were screened over 8 months; 772 from the CEC, 161 from NI, and 907 from the additional neurologist. From the CEC, only 73/772 (9%) were eligible; from NI, 6/161 (4%) were eligible, and from the additional NI neurologist 130/907 (14%) were eligible to participate. From all sources, only 209 (11%) were found to be eligible. Exclusions included: not idiopathic/cryptogenic (970), wrong localization/syndrome (518), age of onset over 35 (289), non-epileptic (179), and no clear diagnosis (98). 388 patients were excluded for more than one reason. Of eligible patients, 31 (less than 2% of all screened) participated. More than half of eligible patients did not participate because they had not yet been contacted by their physician (166). Other reasons included refusal (9), living out of catchment area (2), and requesting compensation beyond protocol (1).

Conclusions: Recruitment for TLE genetic studies can be time consuming and difficult. Even at a major academic surgical epilepsy center, a small fraction of patients screened participate. In our study, overall only 11% of screened patients were eligible to participate, and the most common reason for exclusion of patients was known or presumed symptomatic etiology. Stringent inclusion criteria are important in genetic studies for creating a group of well-characterized subjects with reliable phenotypes, but this may slow recruitment.

Waiting for physicians to contact their patients prior to contact by research staff created the greatest obstacle to recruitment. Obtaining permission from treating physicians to contact patients directly can streamline enrollment, but is not acceptable for all physicians and patients. Broadening recruitment to additional populations may also be helpful.

IMAGE: images/887364_A.jpg

IMAGE: images/887364_B.jpg

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MOLECULAR CLASSIFICATION OF NEONATAL AND INFANTILE EPILEPSIES

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Rationale: Rationale: The revised ILAE classification and terminology (Berg et al 2010; Epilepsia 51:676-685) acknowledges that classification of the epilepsies will in future need to incorporate advances being made in basic neurosciences. Benign Familial Neonatal Seizures (BFNS), Benign Familial Neonatal Infantile Seizures (BFNIS) and Benign Familial Infantile Seizures (BFIS) are currently distinguished by ascending mean age of seizure onset (2-3 days; 11 wks; and 6 mths, respectively), but with overlapping distributions (1 day-6 mths; 2 days to 6 mths; and 2 mths to 20 mths, respectively). Families can be skewed in their clinical manifestations, or isolated cases and small families display only a small range of their potential clinical variability, or different mutations in the same gene vary in expressivity due to the specific mutation, or to affects of modifier loci. This can pose a challenge for clinical diagnoses.

Methods: Methods: Clinical observation will always direct the most appropriate genetic testing, even when clinical descriptors alone cannot clearly delineate the syndromes. Currently, sequencing of either the potassium channel subunit genes KCNQ2 and KCNQ3 and/or the sodium channel gene SCN2A provides molecular discrimination. Utilisation of laboratory based diagnoses where clinical observations alone are not definitive is compatible with the recent ILAE concept of recognising "genetic epilepsies" as a distinct classification.

Results: Results: Previously BFIS cases have been reported with SCN2A mutations prompting SCN2A to be referred to as both a BFNIS and BFIS gene. In our experience, clinically defined BFNS families have for a time been regarded as having SCN2A mutations prompting SCN2A to also be considered as a BFNS gene, until subsequent investigation of the extended family disclosed wider phenotypic variation consistent with BFNIS. These dilemmas are easily resolved. Patients and families previously diagnosed as BFNS, BFNIS and BFIS could be grouped and renamed Familial Infantile Epilepsy (FIE), since onset for all three is before two years of age and the ILAE now suggest "epilepsy" be substituted for "seizures". FIE could be molecularly refined by addition of a suffix, namely FIE:KCNQ2, FIE:KCNQ3 and FIE:SCN1A if or when genetic test results are available. "Benign" in the context of these disorders is a misnomer, as we learn more about the course of these conditions, so that disappears.

Conclusions: Conclusions: Prognosis and treatment can be based on knowledge of the gene and its mechanism of action. The gene for FIE families mapping to chromosome 16 awaits discovery; hence, these families remain as FIE. Overlaps between clinical entities disappear when molecular criteria are included as part of the diagnostic protocol.

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CYP2C9 *2 AND *3 GENOTYPE PREDICTING NON-RESPONSE TO VALPROATE IN PATIENTS WITH EPILEPSY

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Rationale: A large proportion of patients with epilepsy will continue to have seizures despite adequate trials of a range of licensed drugs used singly or in combination. These individuals are regarded as having refractory or drug-resistant epilepsy. Although debate continues about the definition(s) of drug resistance, the complete and permanent control of seizures is not obtained with current therapies in about 30% of patients, adults and children. Although many factors may contribute to variability of clinical outcome in individual patients, unpredictability may, at least in part, result from genetic variation. We aimed to evaluate the association of response to valproate and the frequency variants in the genes IL1A, IL1B, UGT1A4, GSTP1, and CYP2C9.

Methods: A total of 102 children and adolescents with epilepsy (50% male; mean age of 8 years) were genotyped for seven putatively functionally relevant polymorphisms. The sample analyzed consisted of two groups: 51 patients with typical absence responsive to valproate (responders) and 51 patients with refractory epilepsy (non-responders). Genomic DNA was extracted from peripheral blood. Genotyping for the selected polymorphisms (rs1800587, rs1143634, rs2011404, rs1018124, rs1695, rs1799853, rs1057910) were performed using TaqMan® based SNP Genotyping Assays (Applied Biosystems, Foster City, CA, USA). The allele-detection process was performed on a 7500 Real-Time System (Applied Biosystems, Foster City, CA) to determine the allelic discrimination.

Results: Patients heterozygous for CYP2C9*2 and CYP2C9*3 alleles were significantly underrepresented among non-responders (11,4%) to valproate therapy compared to responders (34,1%) [odds ratio (OR) 4.019 (1.18-13.682); P=0.019].(Table) Conversely, others genotype distribution did not significantly differ between responders and non-responders patients. (Figure)

Conclusions: We found CYP2C9*2 and CYP2C9*3 variant alleles carriers were underrepresented among non-responders. These data suggest a higher risk of antiepileptic drug failure, in this case for valproate, in CYP2C9*2 and *3 allele carriers. Our results are in agreement with Ufer M. et al. (Pharmacogenet Genomics. 2009 May;19(5):353-62). Many reports suggest interaction between valproate on cytochrome P450 2C9 (CYP2C9) but the mechanisms are still unknown. Maybe these poor metabolizers (CYP2C9*2 and *3) allele carriers maintains higher drug plasmatic concentrations. A better understanding of the genetic influences on epilepsy.

Financial Support: FAPESP and ABADHS.

IMAGE: images/907506_B.jpg

Figure. CYP2C9 alleles distribution

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A NOVEL GENE LOCUS OF PHOTOGENIC CHILDHOOD ABSENCE EVOLVING TO JME

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Rationale: To identify a novel gene for photogenic childhood absence evolving to JME.

Methods: Whole genome scan with 440 microsatellites was performed in one large family ascertained through a proband with photogenic childhood absence evolving to JME. (four generations with 46 members of which 11 were clinically affected and one EEG affected). Two point linkage analysis using autosomal dominant model, 70 % penetrance, disease allele frequency of 0.001 and phenocopy and gene mutation rates of 1% was performed. The segregated hot-spot was narrowed by recombination mapping and constructing haplotypes using SNPs.

Results: The maximam LOD score was 2.7 (Zmax, theta=0, m=f) for microsatellites for chr 10q11.23-10q21.3 (D10S1220, D10S1225). Advanced study by haplotypes and SNPs narrowed the segregated hot-spot to 1.5 cM.

Conclusions: Our result suggests a novel gene for photogenic CAE evolving to JME located within chr10q11.23. Targeted genomic capture and exon sequencing is ongoing for this region to discover the new epilepsy gene.

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THE EFFECT OF SEIZURES IN HEALTH-RESOURCES UTILIZATION IN PATIENTS WITH ISCHEMIC STROKES: A CANADIAN MULTI-CENTER PROSPECTIVE STUDY

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Rationale: We have previously reported that the presence of seizures after stroke was associated with increased mortality. But limited information is available about the impact of seizures on health-resources utilization after ischemic strokes. Our aim was to assess the impact of seizures in health-resources utilization, in patients admitted to a hospital with acute ischemic stroke.

Methods: This cohort study included consecutive patients with acute ischemic stroke between July 2003 and March 2008 from the Registry of the Canadian Stroke Network, the largest clinical database of patients in Canada with acute stroke seen at selected acute care hospitals. A step-by-step approach with the inclusion of interaction terms using logistic regression analysis was used to determine whether the presence of seizures was associated with health-resources utilization after adjusting for other relevant demographic and clinical characteristics.

Results: Amongst 10261 patients included in the study, seizures occurred in 208 (2.03%) patients with ischemic stroke. A higher number of patients with seizures were admitted to the ICU (20.7 vs. 8%, p< 0.001), although there were no differences in the number of patients admitted to the stroke unit (p=0.06). A higher number also required assessment by speech therapy (70.7 vs. 63.6%, p=0.03). No differences among the groups were found in regards to assessments done by physical (p=0.44) and occupational therapy (p=0.32). The mean length of stay was longer for those with seizures compared to those without: 25.8 (+/- 2.5) vs. 14.8 (+/- 0.2) days (p<0.001). Discharge to an long term care facility was seen in 19% of patients with seizures (vs. 10% in those without seizures, p<0.001).

Conclusions: Seizures in patients with ischemic stroke increased some health-resources utilization. This information may be useful to establish quality improvement strategies targeting stroke-patients with seizures.

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RACIAL DISPARITIES OF SEIZURE CARE IN THE EMERGENCY DEPARTMENT

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Rationale: Blacks and Hispanics have a twofold higher prevalence of epilepsy when compared to Whites, but tend to receive less state of the art therapies. A prior study analyzed Emergency Department (ED) visits for seizure using a large national database. Their analysis found that Blacks were less likely to be admitted to the hospital, and that Blacks, Hispanics, and patients without private insurance were less likely to receive neuroimaging. We reviewed all ED visits for seizure during one year to see if disparities in treatment were similarly noted and, if present, to investigate potential reasons for them.

Methods: This study was approved by the Partners Human Research Committee. We retrospectively reviewed the electronic medical records of patients seen in a large urban tertiary medical center ED from 1/1/2008- 12/31/2008 with ICD-9 codes for epilepsy, seizures, myoclonus, and convulsions (345, 333.2, and 780.3). Only visits with seizure as the precipitating factor were included. Data were collected on race, insurance [private vs. non-private (Medicare, Medicaid/MassHealth, Commonwealth Care, self pay, and no insurance/ health safety net)], frequency of ED visits in the year, probable cause of seizure, and ED management (lab results, medication management, neuroimaging, and admission). Statistical comparisons used generalized linear mixed models accommodating multiple visits per patient (SAS 9.2).

Results: Of 38,879 total ED visits, there were 559 visits for seizure (1.5%) made by 442 patients. Of these 442 patients, 267 (61%) were white, and 170 (39%) were non-white (Black n=100; Hispanic n=59; Asian n=11). The mean age was 48 years, and 51% were male. Non-white patients were less likely to receive neuroimaging in the ED (p = 0.02), and were less likely to be admitted to the hospital (p < .0001). Patients who did not have private insurance showed a trend towards less neuroimaging (p = 0.06), but were just as likely to be admitted as those with private insurance (p = 0.46). Non-whites were more likely to have multiple ED visits for seizure within the year (p=0.001), and to have a history of epilepsy (p=0.01). Whites and non-whites were equally likely to have electrolytes, a toxicology screen, and/or an anti-epileptic drug (AED) loaded. While both groups were equally likely to present for seizure without a clear cause, non-whites were more likely to have not adhered to their medication regimen (missed or ran out of AEDs) as the cause of their seizure visit (p=0.001).

Conclusions: Seizures are a common cause of ED visits in our tertiary hospital. Non-whites are less likely to have neuroimaging performed in the ED and less likely to be admitted to the hospital. This racial disparity was not fully explained by insurance status. ED management

was otherwise similar for both groups. The combination of non-adherence and repeat ED visits for seizure within the year for the non-white patients suggests a difference in ED utilization between racial groups.

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MEASURING PARENTS' PERCEPTIONS OF PATIENT-CENTERED CARE IN CHILDHOOD EPILEPSY: RELIABILITY AND VALIDITY OF THE PATIENT PERCEPTIONS OF PATIENT-CENTEREDNESS (PPPC) QUESTIONNAIRE

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Rationale: Patient-centered care is widely advocated as a preferred model of clinical care. Positive interaction with physicians may be an important aspect influencing family adjustment to chronic disease. To understand the extent to which patient-centered care is practiced and its impact on patient outcomes, it is essential that the measures used to assess this construct are reliable and valid. This study assesses the psychometric properties of the Patient Perceptions of Patient-Centeredness (PPPC) questionnaire as administered to parents of a sample of children newly diagnosed with epilepsy.

Methods: Data were obtained from the Health Related Quality of Life in Children with Epilepsy Study (HERQULES), a national prospective cohort study of children 4-12 years old with new-onset epilepsy. Mailed questionnaires were completed by parents at baseline (n=374), 12 months (n=304) and 24 months (n=295) later.

Internal consistency reliability was assessed at each time point using Cronbach's alpha. Test-retest reliability was assessed using an intraclass correlation coefficient on a subsample of n=21 paired questionnaires. Construct validity was assessed by testing hypotheses regarding the expected relationships of perception of patient-centered care with parent concerns about their child, and with physician's gender.

Results: Cronbach's alpha coefficients for the PPPC showed acceptable internal consistency reliability at all time points (á>0.70). Test-retest reliability was moderate (ICC=0.679). Spearman correlations between parental concern about emotional well-being and patient-centered care were stronger at 24 months than at baseline ($r_{baseline}$=0.108, $r_{24\ months}$=0.191, p>0.1). Parents rated female physicians' care as significantly more patient-centered than that of male physicians at 12 months and 24 months ($t_{12\ months}$=-2.08, $t_{24\ months}$=-2.04, p<0.05).

Conclusions: The Patient Perceptions of Patient-Centeredness (PPPC) questionnaire demonstrated good internal consistency reliability and test-retest reliability when administered to parents of children newly diagnosed with epilepsy. The PPPC also demonstrated reasonable construct validity in this population. If further assessments of the psychometric properties of the PPPC questionnaire within the context of pediatric epilepsy are consistent with the current results, it may be a valuable research and clinical tool for measuring the extent to which health care provided to children with epilepsy is perceived by parents as patient-centered.

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EPILEPTOLOGIST ADHERENCE TO DEPRESSION TREATMENT GUIDELINES

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Rationale: Optimal epilepsy outcome depends on recognition and effective treatment of co-morbid depression. This study assessed epileptologist adherence to depression treatment guidelines.

Methods: The study population is 1,714 patients seen from Oct 2008 to Jun 2009 in a tertiary epilepsy outpatient setting. Patients routinely complete a health status survey before each visit using touch-screen computer technology. The Patient Health Questionniare-9 (PHQ-9), one of the survey instruments, is used for depression screening. Each of the 9-items is rated from 0-3 resulting in a total score of 0 to 27. A score of 10 or more is significantly correlated with a DSM-IV diagnosis of major depression. Item 9 of the PHQ-9 assesses presence of suicidal ideation (SI). Survey responses are automatically uploaded to the electronic medical record for inspection by the patient's assigned clinician. A PHQ-9 total score of >10, or an item-9 rating of 1, 2 or 3, triggers a flag that alerts the clinician to the possible diagnosis of depression and/or elevated suicide risk. Both investigators (EF and GET) reviewed the records of all patients who endorsed suicidal thoughts on item 9 and a random sample of the records of all patients with PHQ-9e"10. Records were reviewed for evidence of adherence to depression treatment guidelines including documentation that the clinician addressed PHQ-9 results with the patient, initiated antidepressant medication, appropriately adjusted existing antidepressant medication, and/or referred the patient to another clinician (behavioral expert, neurologist, or primary care clinician) for further depression care. Data were derived from a single encounter per patient.

Results: 494 patients (28.9%) had a PHQ-9e"10 and 192 (11.2%) endorsed some degree of suicidal ideation. The records of 228 patients were reviewed including the 192 with SI and 36 with pHQ-9e"10 and no SI (item 9 score of 0). Ten clinicians, including nine epileptologists and one epilepsy nurse practitioner saw a mean 22.8 patients per clinician (median=24; range, 6 - 56). Mean rate of appropriate documentation per clinician was 82% (median=85%, range, 59%-100%). 136 patients (60%) were not on antidepressant and only 11 (8%) were advised to start medication. Of the 92 patients already on antidepressant medication treatment modification was recommended to only 9 (10%). Many of these patients, however, were referred appropriately for further evaluation and treatment of depression resulting in 179 instances in which patient was judged to have received appropriate depression care (mean, 78.5%; range, 60-100%).

Conclusions: Epilepsy clinicians fell short of satisfying the portion of the guideline that addresses appropriate prescription of antidepressant medication. However, in most of these instances, clinicians appropriately delegated antidepressant management to other providers resulting in a nearly 80% rate of guideline adherence. This serves as a benchmark against which to judge future depression care by these same clinicians and those in other neurological disciplines.

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KNOWLEDGE OF WOMEN'S ISSUES RELATED TO PREGNANCY IN EPILEPSY: A SURVEY OF HEALTH CARE PROFESSIONALS

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Rationale: New guidelines have been established by the American Academy of Neurology regarding issues related to pregnancy for women with epilepsy. It is unclear what the level of awareness of the updated guidelines is amongst health professionals involved in neurological care. Our objective was to assess the current level of knowledge regarding women's issues related to pregnancy in neurologists and neurology residents.

Methods: A questionnaire was developed to assess physician knowledge of current guidelines for women with epilepsy and pregnancy in the Calgary Health Region, Emphasis was placed upon knowledge of pregnancy-related risks associated with specific anti-epileptic drugs. The questionnaire was distributed in person to neurologists and neurology residents in one tertiary care centre. Descriptive statistics were obtained for all variables. Independent sample t-tests were used to assess the association between level of practice and knowledge. Pearson's correlation was used to assess the association between the proportion of epilepsy patients in one's practice and knowledge of women's issues in epilepsy.

Results: Thirty-three physicians have completed the survey (response rate = 94.3%), with an average score of 51.36%. Staff physicians comprised 25 out of 33 completed surveys. Residents were more likely to state that this information was important to their practice than staff physicians, but no significant difference was noted in their overall scores ($t = -0.408$, $p=0.686$). No significant difference was noted in final score between males and females ($t= - 0.149$, $p=0.882$). A significant positive correlation (Pearson's correlation = 0.455, $p=0.025$) was noted between the proportion of epilepsy patients in one's practice and final score. Despite the fact that the majority of respondents were not epileptologists, and only followed patients with epilepsy while they were on the inpatient neurology ward service, 94% of them were able to correctly identify that valproate substantially increases the risk of major congenital malformations; however, only 55% were aware that this drug crosses the placenta. Only 40% of physicians knew that there was good evidence of a dose-response relationship between valproate and the risk of major congenital malformations, and only 6% were aware of a similar relationship for lamotrigine. Additionally, a quarter of physicians knew that women should be seizure-free for 9 months prior to conception to ensure a high likelihood of a seizure-free pregnancy.

Conclusions: More knowledge translation efforts are required to increase physician knowledge of issues related to pregnancy for women with epilepsy. Increased awareness and applications of the guidelines in practice should result in provision of better care for women with epilepsy of reproductive ages. Steps need to be taken to address this knowledge gap.

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HEALTHCARE COSTS FOR CHILDREN WITH SEIZURES PRESENTING TO LE BONHEUR CHILDREN'S HOSPITAL EMERGENCY DEPARTMENT

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Rationale: 1) To determine the financial cost for patients presenting to the emergency department with febrile seizures, complex febrile seizures, new onset seizures and recurrent seizures.

2) To determine the length of stay (LOS) in the Emergency Department of these patients.

Methods: All patients between the ages of the 0-18 years of age presenting to the Emergency Department in Le Bonheur Children's Hospital with simple febrile seizures, complex febrile seizures, new onset seizure and recurrent seizures not requiring hospital admission were included in this retrospective chart review for the month of January of 2008. Transportation charges, physician charges, laboratory charges, and facility charges were assessed for each patient. We were unable to obtain Radiology physician, drug levels, and medication charges, so these were not included.

Results: Of the 126 charts reviewed, 101 were eligible and included in the study. Twenty-five patient charts were excluded from analysis because two patients had non-epileptic seizures, five patients were diagnosed with "seizure-like activity", two charts were missing physician notes, and 16 patients had an underlying seizure disorder but were being evaluated for another medical problem not associated with their seizure disorder. LOS for new onset simple febrile seizures versus recurrent simple febrile seizures is significantly longer with new onset febrile seizures requiring more time to evaluate ($p=0.04$ (95% CI 2-110 mins)) with an average difference of 56 minutes.

Conclusions: Children presenting to the Emergency Department with seizures can generate significant healthcare costs. Seizures are frightening for the observer but are generally short and not harmful to the patient. Healthcare costs could potentially be reduced with seizure education, home medication for emergency use, and improved access to emergency advice. In addition, visitation to the ER could be avoided resulting in less impact on the family and the ER. This is particularly pertinent for patients with recurrent seizures. Further evaluation with an active intervention in a prospective study is required.

Cost and Length of stay for children with seizures presenting to the ED

IMAGE: tables/907030_T1.jpg

3.329

PATIENT PERCEPTIONS OF INFORMATION NEEDS FOR TLE SURGERY DECISIONS

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Rationale: Whether to have temporal lobe epilepsy (TLE) surgery remains a complex decision. Patient focused decision aids, containing information on risks and benefits of treatment interventions, have been shown to increase patient knowledge and facilitate shared decision making between patients and physicians. Such a tool does not exist for TLE surgery. The purpose of this study was to describe TLE patients' information needs related to their decision-making process regarding TLE surgery and to identify the potential for a patient decision aid to assist in meeting these needs.

Methods: A sample of TLE patients who have already had surgery was invited to participate in a focus group via a letter invitation. Patients were excluded if they had dementia, developmental delay, or other medical or neurological problem that would preclude participation in a focus group. Focus group questions included how patients gained knowledge about TLE surgery, what type of information they wanted to know, and what they would suggest for inclusion in a patient decision aid. The focus group was tape recorded, and verbalizations were thematically analyzed. Based upon the data, the authors generated ideas about the type of patient decision aid that could facilitate TLE patients' epilepsy surgery decision-making process.

Results: The patients (N=7) were 70% male ranging in age from 28-67. Thematic analysis revealed that the majority of the patients had not been told that epilepsy surgery was a possible intervention for them by their treating doctors. Most described their epilepsy as having severely worsened their quality of life, so on their own, they then used the Internet, read books, or attended patient-oriented information sessions to seek additional potential treatment options. Mostly through word-of-mouth from their family or friends, many then self-referred themselves to an academic referral center for a second opinion. The physicians at the academic referral center further augmented their knowledge about the risks and benefits of TLE surgery.

Participants described their information needs in two broad categories: experiential and factual. For example, one participant expressed experiential information needs as: "Patient's testimonials, capturing people's experience in a way that it can be personally shared with others." Patients also desired factual or quantitative benefit and risk information, but in particular, individualized to specific patients, e.g., left versus right TLE. Most patients felt that a patient decision aid that included such information could be quite helpful when delivered through the use of video clips and the Internet.

Conclusions: TLE patients expressed concern regarding the limited information they received about their treatment options from their doctors. This prompted them to seek information on their own using alternative sources such as books and the Internet. They also identified types of information that TLE patients would find useful and ways in which information could be delivered in a patient decision aid, designed to facilitate the decision-making process for TLE surgery.

3.330

EFFECTIVE STRATEGIES TO IMPROVE EPILEPSY NURSING KNOWLEDGE PRIOR TO THE DEVELOPMENT OF AN EPILEPSY MONITORING UNIT AT A COMMUNITY HOSPITAL

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Rationale: Nursing knowledge of epilepsy is a critical component in the development of an Epilepsy Monitoring Unit (EMU). Studies assessing baseline nurses knowledge of epilepsy are scarce. As part of the development of an EMU at a 300-bed community hospital, a 3-hour nurse focused epilepsy education program was provided by an epileptologist and an experienced epilepsy nurse from an associated Academic Medical Center (AMC). We report overall nursing knowledge of epilepsy before and after the education program.

Methods: Ten medical and surgical nurses with an average of 13.9 years experience attended the epilepsy training course. The course included epilepsy case presentations, an overview of a nurses role in the EMU, seizure documentation, epilepsy nursing assessment, observation of report at shift change, and a tour of the EMU monitoring room. A knowledge questionnaire was provided before and after the course to compare knowledge of epilepsy.

Results: 10/10 nurses took the pre-test and 7/10 took the post test. Of those that took the pre-test, 38% (10/26) of the questions were scored incorrectly. Questions that were commonly scored incorrectly prior to the course were: 1. percentage of population with seizure activity, 2. description of seizures as stereotypical and paroxysmal and 3. percentage of patients who have adequate control of their seizures. Of the 7/10 nurses who took the post test, 23% (6/26) of the questions were scored incorrectly. Questions that were commonly scored incorrectly after the training course were: 1. Common age of epilepsy onset, 2. medications used to treat serial seizures and 3. percentage of patients who have adequate control of their seizures.

Conclusions: Baseline epilepsy knowledge is essential to the delivery of quality patient care in the EMU. After the training course, trends toward increased knowledge of epilepsy were reached. However, despite the highly experienced medical surgical nursing staff, and their attendance at the epilepsy training course, epilepsy knowledge deficits were identified. As a result, further educational courses will be given prior to the opening of the EMU.

3.331

QUALITY IMPROVEMENT IN THE EPILEPSY CLINIC

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Rationale: The American Academy of Neurology (AAN) Subcommittee on Quality Measurement and Reporting is in the process of establishing practice requirements for neurologists specializing in the care of epilepsy patients. Proposed requirements include documentation of 1) seizure type, 2) frequency, 3) etiology/syndrome, 4) EEG results, 5) neuroimaging findings, 6) antiepileptic drugs (AEDs), 7) drug side effects, 8) candidacy for surgery, 9) safety/driving issues, and 10) women's issues (including contraception, vitamin supplementation, and bone health) for every new epilepsy patient evaluated. These requirements may have implications on maintenance of certification. The purpose of this quality improvement study is to establish an effective method of documenting the essential elements in the evaluation of new epilepsy patients.

Methods: A one-page questionnaire was developed to incorporate the above 10 elements and given to new patients evaluated in the Mayo Clinic Arizona Epilepsy Clinic for a one month period of time, May 2010. A retrospective control group was established, including all new patient evaluations conducted in May 2009, for comparison. Epilepsy and indeterminate spells were included in the analysis while patients with syncope or other imitators of epilepsy were excluded. Each encounter was reviewed and scored on a 10-point scale, with one point given for the documentation of each item in the proposed requirements listed above. The two groups were analyzed.

Results: Analysis of the retrospective control group demonstrated an average score of 7.0 out of 10 for each chart reviewed. The most frequently documented items included seizure frequency (90.5%), previous EEG results (95.2%), and antiepileptic medication use (90.5%). The least documented items included candidacy for surgery (33.3%) and safety issues (38.1%). Although women's issues appeared to be adequately documented (71.4%), it should be noted that documentation was considered adequate either if the patient was male, or if only one of the subtopics were covered. Documentation from the prospective questionnaire group was adequate for all charts, since when instructed, patients were faithful in completing the questionnaire.

Conclusions: The AAN is developing methods to improve practice standards across all specialties, including epilepsy. Standardizing practice will lead to improved quality in patient care and subsequently translate into better outcomes for patients. In this single-center study, the retrospective data suggests that there is opportunity for improvement in discussing and documenting several key elements including: patient safety issues (including driving), women's issues, and documenting the patient's candidacy for epilepsy surgery. Novel techniques can be implemented to improve the discussion and documentation of these important patient discussions into clinical practice. This study demonstrates that a simple questionnaire is effective in increasing compliance towards the AAN epilepsy requirements, in turn improving the care of people with epilepsy.

3.332

USING A STANDARDIZED ASSESSMENT TOOL TO MEASURE PATIENT EXPERIENCE ON A SEIZURE MONITORING UNIT COMPARED TO A GENERAL NEUROLOGY UNIT

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Rationale: Seizure monitoring unit (SMU) research typically focuses on its diagnostic utility and optimizing medical management of epilepsy. In order to best achieve these outcomes, it is imperative that the safety and quality of care be optimal. This study reports on an ongoing initiative that uses a standardized assessment tool to measure an important quality indicator of care: patient experience.

Methods: The Hospital-Consumer Assessment of Healthcare Providers and Systems (H-CAHPS), a 27-item survey endorsed for use in acute care hospitals by the Agency for Healthcare Research and Quality, is telephone-administered post-discharge to a random sample of patients as part of the standard quality and safety monitoring of care in our setting. Sixty-eight percent of patients from our 4-bed SMU and 10% of General Neurology Unit (GNU) patients are assessed using the H-CAHPS. Key quality indicators measured by this scale include: responsiveness of nursing staff (e.g., after patient call buttons have been pressed), physician communication (e.g., whether doctors invited patients to ask questions about their care), and patient involvement (e.g., whether patients believed they were involved in decisions about their care).

Results: Data from a 33 month period (January 1, 2007 - September 31, 2009) were reviewed, encompassing 217 SMU admissions (59.4% women) and 317 GNU admissions (56.2% women). The average age of SMU patients was 14.7 years younger (54.8 years for GNU vs. 40.1 years for SMU, $p<.001$) and the length of stay 4.2 days longer than for GNU patients (5.5 days for GNU vs. 9.72 days for SMU, $p<.001$). Across both units, lower education ($p<.05$) was associated with more favourable hospital experience ratings. SMU patients provided lower overall health ($p<.05$) and overall mental health ratings ($p<.001$) compared to the GNU. Regarding our key quality indicators, the SMU patients gave the hospital a better overall rating ($p<.05$) and the nursing staff were perceived to be more responsive to the call button on the smaller SMU than on the GNU ($p<.001$).

Conclusions: Managing quality by systematically measuring and monitoring key indicators facilitates strategic planning, as well as prioritization of quality improvement and safety initiatives for an SMU. This project demonstrates that using a standardized hospital-based patient experience measure has utility in comparing the standard of care on an SMU to other units. Prospectively assessing patient experience of the SMU over time could assist with providing benchmarks for quality patient-centered care. More work is required to determine the ongoing utility of using H-CAHPS to monitor our responsiveness to patient concerns.

3.333

STAFF EXPERIENCE AND SATISFACTION WITH WORKING ON A SEIZURE MONITORING UNIT

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Rationale: Research examining staff experiences on Seizure Monitoring Units (SMU) is sparse. General healthcare research demonstrates that having satisfied staff predicts higher patient satisfaction and outcomes, with teamwork and autonomy being key predictors of staff satisfaction. The purpose of this study was to investigate multidisciplinary SMU staff experiences in order to guide future quality improvement initiatives.

Methods: A staff satisfaction questionnaire used by our local health service to assess hospital-based staff satisfaction was used in this study to specifically assess SMU staff experiences. The survey consisted of 34 questions with a 5-point Likert scale and 2 open response items. Anonymous surveys were completed by SMU staff once a year from 2007-2009. Respondent rate was gathered and differences by discipline and year were examined using Chi square. Responses to key items were examined for differences in satisfaction over the 3 years using repeated measures ANOVA. Four subcategories were created by grouping pertinent survey items: professional development, interdisciplinary teamwork, environment, and patient-centred care. Subcategories were examined for mean differences over time.

Results: Surveys were completed annually by nurses (average n=16), EEG technologists (average n=6), and epileptologists (average n=2), with average response rates of 33.1%, 49.7% and 46.7% respectively. The majority of staff (62.7%) reported that the SMU was a positive place to work. Highest ratings were reported by epileptologists, followed by EEG technologists. While nurses had the fewest positive ratings of the SMU as a place to work, few responded that the SMU was "below average" (12.8%). Subcategory analysis revealed a non-significant trend towards improvement across all four categories over time. Patient-centred care and interdisciplinary teamwork were rated highest by staff and also changed the least over time. In the professional development category, the largest improvement was in the availability of staff training, which may reflect the addition of SMU-specific staff education sessions over time. The SMU environment subcategory was rated the lowest. The item with the most negative responses was space

availability: only 21.5% of staff perceived that the available space was satisfactory in 2009, which was a decrease from 37% in 2008 and 33.3% in 2007.

Conclusions: Staff generally perceived our SMU as a positive place to work, with particular strengths being patient-centered care, interdisciplinary teamwork, and availability of staff training. Key areas for improvement were environmental issues such as space availability. Future research will continue to explore changes in staff experience over time, particularly after implementing quality improvement initiatives addressing staff concerns.

3.334

FACTORS AFFECTING HOSPITAL LENGTH OF STAY FOR PATIENTS WITH EPILEPSY: RESULTS FROM A NATIONAL INPATIENT SURVEY

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Rationale: The purpose of this study was to identify hospital characteristic factors affecting length of stay by patients with epilepsy. We used the revised theoretical model of healthcare access and utilization, the Andersen Behavioral Model.

Methods: This study used information on hospital discharges of patients with epilepsy (PWE) extracted from the 2004 Healthcare Utilization Project's (HCUP) Nationwide Inpatient Sample (NIS). To extract the epilepsy population we used the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes. The principal objective was to analyze the effect of patient, hospital and geographic characteristics on the Length of hospital stay (LOS) by PWE. To explain the variability of LOS, we have used Inverse Gaussian Regression. Regression models incorporated the predisposing factors (age, gender), enabling factors (patient characteristics: admission source, payer information, median household income; hospital characteristics: control/ownership, geographic region, teaching status, location, bed size), and illness/need factors (admission type, number of medical diagnoses, number of medical procedures and severity measures) to identify how these variables influence the LOS for PWE admitted to hospitals within the sampling frame.

Results: The data set for the analysis totaled 261, 024 weighted hospital discharges of patients with a primary diagnosis of epilepsy. Hospital characteristic factors that significantly affected LOS were: private-non-profit (voluntary) hospitals shorter LOS than public hospitals (OR: .924, [95% CI .854 - 1.000], $p < 0.05$); non-teaching hospitals shorter LOS than Teaching (OR: .943, [95% CI 0.896 - 0.993], $p < 0.05$); Rural hospitals shorter LOS than Urban (OR: .856, [95% CI .807 - .908, $p < 0.001$]; Region - Midwest, South and West shorter LOS than Northeast (OR: .836, .879, and .885) [95% CI .796 - .879], [95% CI .836 - .925], and [95% CI .822 - .953], all values respectively and $p < 0.001$; small and medium bed sized hospitals shorter LOS than large (OR: .917 and .944, [95% CI 0.872 - 0.963 and 0.909 - 0.981], respectively, and $p < 0.05$.

Conclusions: Controlling for several indicators, non-government hospitals report shorter length of stay. Patients with epilepsy are primarily utilizing large bed sized, teaching hospitals, which tend to be located in urban areas and report longer length of stay. In order to receive treatment for complex and sometimes severe medical condition, PWE may be seeking hospitals with greater scale and service capacity, i.e., video monitoring or surgical evaluation, as examples. Policy implications may effect a reduction in disease burden for large bed sized, teaching hospitals. Possible clinical collaborations would be warranted with neurologists affiliated with non-teaching, small or medium bed sized hospitals to implement more preventative practices, i.e., routine monitoring of therapeutic antiepileptic drug (AED) levels. Collaborations would be necessary in an effort to prevent possible lengthy hospital stay, i.e., AED dose adjustment/toxicity.

3.335

A CONSUMER GENERATED SELF-MANAGEMENT INTERVENTION MODEL

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Rationale: The 2003 Living Well with Epilepsy II Conference yielded recommendations regarding the development of self-management programs for people with epilepsy. The University of Washington is 1 of 5 sites in the Centers for Disease Control-funded Managing Epilepsy Well network initiating research in this area. A paucity of consumer needs assessment data in epilepsy self-management programming lead the aim to involve consumers in program development versus rely solely upon professional judgment.

Methods: Literature review was used to create a consumer needs survey. Next, 2 focus groups were held with adults with epilepsy (n = 20) to validate contents. Qualitative responses were recorded and used to refine survey items, which included demographic, physical and mental health, and intervention format items, as well as a problem rating scale. A total of 270 surveys were mailed to adult outpatients from Epilepsy Foundation Northwest support groups (n =20), Swedish Hospital Epilepsy Center (n =125), and UW Regional Epilepsy Center (n =125).

Results: A total of 165 (61%) surveys were collected. Respondents were a mean age of 41 years; 43.6% male; and a mean age of 22.6 years at the time of epilepsy diagnosis. Over 40% reported a history of depression treatment. Over 30% were employed full-time; 39.8% were underemployed; 23.3% received disability income due to a seizure condition. Multivariate linear regression was used to identify predictors of life adjustment (perceived health, happiness, and life satisfaction). For all 3 outcomes the Personal Health Questionnaire-9 (PHQ-9) depression score was the best predictor (Table 1). For happiness and life satisfaction, the PHQ-9 out-performed all other variables such that none of them improved the predictive power of the model. However, by replacing the PHQ-9 score with a dichotomous measure of major depression, additional variables contributed to the predictive power of the multivariate model. Specifically, major depression, anxiety, and cognitive problems predicted happiness. Income, major depression, anxiety, and cognitive problems predicted life satisfaction (Table 2). Secondary analyses compared problem ratings of respondents with depression or cognitive problems to respondents without these concerns. The impaired respondents were less likely to be employed and reported significantly greater difficulty with independent living, work, socializing, epilepsy management, health and well-being, and medical care. Regarding intervention format, respondents prefer in-person individual or group sessions that meet for 1 hour on a weeknight and are lead by a physician or a professional plus lay person with epilepsy.

Conclusions: Health and well-being are influenced by depression and cognitive problems. These issues seem to influence the perceived problems of adults with epilepsy. The concerns of consumers need to

be carefully considered in the development of epilepsy self-management programs. The needs of those with higher levels of depression and cognitive concerns deserve unique consideration as these adults are more likely to have difficulty with adherence to medical regimen and life adjustment.

Table 2: Predictors of Disability Adjustment

IMAGE: tables/906964_T1.jpg

Table 1: Relationship of PHQ-9 Score with Adjustment

IMAGE: tables/906964_T2.jpg

3.336

DEPRESSION IN MOTHERS IN THE 24 MONTHS FOLLOWING A DIAGNOSIS OF EPILEPSY IN THEIR CHILDREN: SURVIVAL ANALYSIS AND RISK FACTORS

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Rationale: Previous research suggests that 12-49% of mothers caring for children with epilepsy are at risk for clinical depression based on self-report measures of depressive symptoms. The objectives of this research were to: 1) prospectively examine the onset of depression in mothers of children newly diagnosed with epilepsy and 2) identify risk factors for mothers developing depression during the 24-month following epilepsy diagnosis in their children.

Methods: Data were obtained from the Health Related Quality of Life in Children with Epilepsy Study (HERQULES), a national prospective study of children 4-12 years old with new-onset epilepsy followed for 24 months. Maternal (age, parity, marital status, education, employment, depressive symptoms), child (age, sex, family history, seizure type, epilepsy classification, duration, medication use, severity, health-related quality of life), and family (functioning, resources, demands, perception of family-centred care, income) variables were examined using mother and neurologist report at baseline, 6, 12, and 24 months. Maternal depression was defined as scoring at or above the threshold for clinical depression (e"16) on the Center for Epidemiologic Studies Depression Scale (CES-D). Depression-free survival was calculated using the life table approach for discrete time whereby mothers depressed at baseline were left-censored. Binary sequence modeling for longitudinal data incorporating the Markovian condition (effect of prior status on current status) was implemented to identify risk factors for maternal depression during the follow-up.

Results: Of 338 mothers who agreed to participate in the study, 38% were depressed at baseline and thus excluded from the survival analysis. By 24 months, 70% of mothers who were not depressed at baseline had not experienced the onset of depression. The probability of onset of depression and associated 95% confidence intervals by 6, 12, and 24 months was 0.13 (0.08, 0.18), 0.12 (0.07, 0.17), and 0.19 (0.10, 0.27), respectively. Of those experiencing onset of depression at baseline, 6, and 12 months, 26%, 12%, and 32% were still depressed at 24 months, respectively. Accounting for prior depression status, risk factors for developing depression during follow-up were maternal age (OR=0.94, p=0.012), number of anti-epileptic drugs child was prescribed (OR=1.41, p=0.004), family functioning (OR=0.83, p<0.001), family resources (OR=0.93, p<0.001), and family demands (OR=1.10, p=0.001).

Conclusions: This study is the first to prospectively document depression in mothers of children with newly diagnosed epilepsy. Over one-third of mothers are at risk for clinical depression when their child is diagnosed with epilepsy and the probability of developing depression after epilepsy diagnosis is relatively stable over time. Given that several of the risk factors identified for maternal depression are modifiable, it is important to consider these as potential targets for clinical intervention to improve the mental health of mothers of children with epilepsy over first 24 months after diagnosis.

3.337

ADOLESCENTS IN TRANSITION: DEVELOPMENTAL AND PSYCHOSOCIAL CONCERNS FOR YOUTH WITH INTRACTABLE EPILEPSY

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Rationale: The childhood onset of intractable epilepsy is often a lifelong condition, thus children must learn to assume responsibility for their own care as they approach adulthood. The purpose of this abstract is to study the developmental and cognitive attributes that contribute to this ability to assume responsibility for their epilepsy care as adults.

Methods: A social worker obtained a psychosocial assessment (PA) in a convenience sample of adolescents with intractable epilepsy seen in our outpatient clinic (5/20/08 -8/30/09). The PA combined HEADSSS screening and anticipatory guidance commonly used in Primary Care with self or parent reported transition-specific knowledge, attitudes, and skills. Information was provided by patients, parents, and medical records.

Results: 30 adolescents were included (16 male, 14 female; 15 Caucasian, 5 African American, 8 Hispanic, & 2 Other). The median age was 15.5y, range 11-23y; 15 < 16 years of age (younger) and 15 > 16 years of age (older). Cognition was assessed as within normal (7), mild to moderate impairment (18), and severe impairment (5). In older patients, cognition was assessed as within normal (3), mild to moderate impairment (10) and severe impairment (2). 23 had special education services in school.

Medical knowledge was based upon the 25 youths who were cognitively able to participate in their care. 17 had a developmentally appropriate understanding of their medical condition for their cognitive level. (9 of 12 younger, 8 of 13 older). 12 knew all of the names of their medications (6 of 12 younger, 6 of 13 older). 18 knew the purpose of their medications, (8 of 12 younger, 10 of 13 older). 5 (all older) had independently met with a medical provider (physician or nurse practitioner) in the last year. 10 acknowledged not adhering to their medication regimen as prescribed in the last year.

16 expressed an interest in intimate relationships, although only 3 acknowledged being sexually active (1 younger, 2 older). 6 acknowledged alcohol use (1 younger, 5 older) and 3 acknowledged drug use (3 older). In the previous 3 years, mental health disorders affected 15 out of 25. Of those 15 patients, 11 had internalizing disorders and 9 had externalizing disorders (5 had both types of disorders).

Conclusions: These data illustrate the types of preparedness issues faced by adolescents with epilepsy as they approach the time when they will assume responsibility for their care. In summary, medical

knowledge did not seem to increase with age and a larger than anticipated number of patients had interest in intimate relationships, drug/alcohol use and mental health needs. Awareness of these issues should help enable providers to screen for medical knowledge, mental health and risk taking behaviors. Ultimately we envision the development and implementation of programs to assist youth with epilepsy as they transition to adult care.

3.338

DEVELOPMENT OF A CONCEPTUAL MODEL FOR THE STUDY OF BREAKTHROUGH SEIZURES IN HOSPITALIZED CHILDREN WITH EPILEPSY AND ASSOCIATED RISK FACTORS

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Rationale: Seizures are one of the top 10 reasons for hospitalization in children but the incidence of seizures in children with epilepsy hospitalized for other reasons is unknown. Breakthrough seizures in children with epilepsy can progress to status epilepticus as well as being disturbing to patients, parents and medical staff. Factors in addition to baseline seizure control may determine whether seizures occur in hospitalized children with epilepsy. Children with underlying neurologic problems are more likely to experience medication errors, more likely to have difficult to control seizures, and more likely to be hospitalized. Study of this topic would benefit from a conceptual model and the development of a data acquisition tool based on the model

Methods: Review of the literature and interviews with stakeholders, including parents of children with epilepsy, nurses, pediatricians, pediatric neurologists, epileptologists, quality improvement experts,and hospital administrators were undertaken to assess the potential causes and significance of breakthrough seizures.

Results: Key informants and the medical literature confirmed that this topic area has been under studied, and is important. Three domains of risk factors for breakthrough seizures emerged: Baseline Patient Risk Factors, i.e. underlying neurologic and systemic problems; Acute Patient Risk Factors, i.e. concurrent systemic illness; and Systems Factors, including medication errors and changes in medication timing. Using MedQuest - Clinical Data Collection Design System (v.720), a medical record abstraction tool was designed to capture these risk factors for each domain together with the outcome of interest: breakthrough seizures and their consequences. The tool also requires all anticonvulsant medication orders and administration times to be captured systematically. This feature avoids requiring subjective decision making by abstractors related to the presence or absence of a medication error. Pilot testing of the tool to abstract data from 30 charts of children with epilepsy admitted for reasons other than epilepsy was successful: salient features of breakthrough seizures documented in the medical record were captured by the tool. Risk factors modeled by the three domains above, including anticonvulsant medication errors, when present in the charts, could be tracked with the tool.

Conclusions: Breakthrough seizures in children with epilepsy admitted to the hospital for reasons other than epilepsy may in part be preventable, but little is known about the scope of this problem, or the factors associated with it. Using a conceptual model as a framework, we have developed a structured medical record abstraction instrument that will permit the collection of data within each of the risk factor domains. The data obtained using this instrument will provide information on the incidence, associated risk factors including medication errors, and consequences of breakthrough seizures.

3.339

DYNAMIC DISINHIBITION OF CORTICAL CIRCUITS

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Rationale: Epileptic syndromes are frequently accompanied by changes in interneuron properties and numbers. Parvalbumin-positive (FS) interneurons exert strong perisomatic inhibition onto cortical pyramidal cells and can veto spike generation. To investigate their influence on cortical circuit properties we dynamically silenced FS interneurons via activation of the light-gated chloride pump halorhodopsin (eNpHR). We hypothesize that silencing of FS interneurons leads to a pronounced enhancement of cortical excitability.

Methods: Mice (3-4 weeks old) expressing cre-recombinase under the control of the parvalbumin promoter (parv/cre-mice) were infected with an AAV vector ("AAV5-EF1a-DIO-eNpHR3.0-EYFP") containing a doublefloxed eNpHR-EYFP construct controlled by the EF-1a promoter. Virus was stereotaxically injected into each hemisphere of the primary somatosensory cortex. Expression efficiency and localization were evaluated using EYFP fluorescence at time points from 10 days to 7.5 weeks post injection. Activation of eNpHR was achieved using a xenon arc lamp that illuminated the slice through the microscope objectives and a 593 +/- 20 nm (yellow) bandpass filter. Inhibitory and excitatory postsynaptic responses were evoked by electrical stimulation and laser-scanning photostimulation/glutamate uncaging (LSPS), and cells were recorded in current and voltage clamp using standard techniques.

Results: Strong EYFP expression was detected up to 1 mm from the injection site. Healthy fluorescent cells were observed 2-4 weeks post injection, but by 5 weeks post injection, many strongly fluorescent cells had formed inclusion bodies and were no longer suitable for electrophysiological recordings. Subsequent experiments were therefore conducted 2-3 weeks post injection. Fluorescent cells had light-activated currents of -195 +/- 65 pA (n=14), corresponding to a hyperpolarization of 24 +/- 10 mV. Stimulation in layer 2/3 elicited complex postsynaptic responses in layer 5 pyramidal cells, consisting of an early EPSC and a later IPSC, which presumably originated via mono- and disynaptic activation, respectively. In the presence of yellow light the IPSC component was reduced or absent in over 50% of recorded cells. In current clamp recordings, repetitive activation of eNpHR by trains of yellow light caused a 2-3-fold increase in spike output at all stimulation frequencies tested (10, 50 and 100 Hz).

Conclusions: These experiments demonstrate the feasibility of a) directing eNpHR expression to FS cells in somatosensory cortex and b) eNpHR mediated disinhibition of pyramidal cells. These methods can now be used to investigate the specific role of FS interneurons in controlling epileptiform activity in slices, and seizures in vivo.

3.340

ABERRANT INTEGRATION OF POSTNATALLY GENERATED NEURONS IS SUFFICIENT TO CAUSE EPILEPSY

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Rationale: Adult generated hippocampal dentate granule cells have been implicated in the development of epilepsy. Following an epileptogenic brain insult, these cells integrate abnormally, leading to characteristic pathologies of the epileptic brain, including the appearance of ectopic cells, cells with aberrant basal dendrites and mossy fiber sprouting. Recurrent excitatory circuits created by these pathologies are hypothesized to promote hyperexcitability and seizures. Direct evidence in support of this hypothesis, however, is limited.

Methods: Here, we sought to determine whether abnormal granule cells are sufficient to cause epilepsy. Using conditional, inducible triple-transgenic Gli1-CreERT2 X PTENflox/flox X GFP reporter mice we were able to selectively disrupt the development of postnatally generated neurons. Triple transgenic animals were treated with tamoxifen on P14, leading to the deletion of PTEN (phosphatase and tensin homologue) and activation of GFP expression in a subset of subgranular and subventricular zone progenitors.

Results: PTEN deletion was highly selective, with a subset of granule cells and olfactory neurons being the only neuronal populations affected in the CNS. PTEN deletion from granule cells reproduced key abnormalities of the epileptic brain, including formation of basal dendrites, ectopic migration to the hilus, and mossy fiber sprouting. Acute hippocampal slices prepared from PTEN deleted animals revealed hyperexcitability in this region. Moreover, animals exhibited longer evoked seizures when challenged with flurothyl. Finally, 24/7 video-EEG monitoring confirmed that these animals were spontaneously epileptic, exhibiting frequent seizures by three months of age.

Conclusions: Abnormal granule cells are a hallmark of temporal lobe epilepsy, and are present in both epileptic animals and humans. For decades, it has been unclear whether these abnormal cells are a cause or consequence of epilepsy. The present study provides new evidence indicating that disruption of postnatally generated neurons is capable of causing epilepsy, and morphological and physiological data strongly implicates hippocampal granule cells, rather than olfactory neurons, in this process. Future studies will focus on determining whether these cells are necessary for epileptogenesis.

3.341

NRSF / REST DEPENDENT AND INDEPENDENT GENE PATHWAYS IN EPILEPTOGENESIS

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Rationale: A number of receptors (e.g., GluR2), ion channels (e.g., HCN1) and transporters (e.g., Kcc2) regulated by the transcriptional repressor NRSF have recently been found to be altered in the epileptic hippocampus. This suggests that repression by NRSF may define a general mechanism by which expression of gene clusters crucial to normal neuronal function might be deranged after insults that promote hyperexcitability and spontaneous seizures.

Methods: Genome-wide expression analysis was performed using Illumina RatRef-12 Expression Beadchips. Experimental groups included controls and rats that experienced kainic-acid-induced status epilepticus (KA-SE). Control and KA-SE groups were treated with oligodeoxynucleotides (ODNs) comprising either the NRSE sequence (as a 'decoy' preventing NRSF binding to its cognate DNA-binding sequence) or a scrambled sequence. In all cases, the CA1 region of the hippocampus was resected two days after KA-SE and mRNA recovered.

Results: 470 genes were repressed by kainic-acid-induced status epilepticus (KA-SE). Of these, 39 contained an NRSE, including, KCC2, TAP1, Kv3.2, NELL1, Grik5, GluR2, NMDA receptor type 2A, SCN3B, GLRA2, KCNIP2, and HCN1. In total 49 ion channels were reduced, of which 22 have a functional NRSE. Treatment with NRSE ODNs left 347 genes repressed, but only 2% contain putative NRSE binding sites. Pathway and cluster analyses showed that ion channels were commonly reduced by KA-SE and rescued by the ODNs. Another major cluster of these NRSF dependent genes is that of calcium binding proteins. NRSF independent gene changes were manifest after KA-SE. These included gene clusters related to stress response and inflammation. Functionally, administration of NRSE ODNs to KA-SE attenuated subsequent hippocampal hyperexcitability and the severity of the resulting epilepsy.

Conclusions: (1) NRSF dependent and independent changes in the expression of gene clusters are provoked by insults resulting in epilepsy.

(2) Rescue from repression, using NRSE ODNs is relatively selective for NRSE-containing genes.

(3) This rescue attenuated the conversion of the hippocampal network into a hyperexcitable one, and the generation of epilepsy, suggesting that NRSF might be a 'master switch' in the coordinated program that promotes hyperexcitability after KA-SE and similar insults.

Therefore, the selective suppression of the function of specific transcription factors, followed by genome-wide analysis provides a powerful tool to uncover genes that are crucial for epileptogenesis and might be therapeutic or preventive targets.

3.342

ABERRANT MOSSY FIBER SPROUTING PREFERENTIALLY INNERVATES IMMATURE CELLS IN A RODENT MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: Aberrant dentate granule cell (DGC) mossy fiber sprouting (MFS) into the dentate inner molecular layer is among the many types of structural plasticity observed in hippocampal tissue from patients with temporal lobe epilepsy (TLE) and animal models of the disease. MFS is known to result in the formation of de novo excitatory connections, primarily onto DGCs [1]. These connections are

hypothesized to play an important role in the formation of aberrant synchronicity of DGCs that may contribute to seizure activity in the epileptic brain. Our recent work suggests that immature or newborn DGCs, rather than pre-existing DGCs, give rise to MFS in the pilocarpine model of TLE [2]. Whether DGCs also show an age-dependent susceptibility for innervation by sprouted mossy fibers is unknown. We hypothesized that immature DGCs are more likely to be innervated by sprouted mossy fibers.

1. Buckmaster, P.S., G.F. Zhang, and R. Yamawaki, J Neurosci, 2002. 22:6650-8

2. Kron, M.M., H. Zhang, and J.M. Parent, J Neurosci, 2010 30:2051-9

Methods: To investigate this idea, we birthdated DGCs by stereotaxic injection of GFP-expressing retrovirus into the dentate gyrus of rats at specific ages between postnatal day (P) 7 and 60, induced status epilepticus (SE) with systemic pilocarpine at P56 and killed animals 4-10 weeks after SE. Mossy fiber synapse formation was assessed by double-label immunofluorescence for zinc-transporter member 3 (Znt3), which labels mossy fiber boutons, and GFP. Confocal microscopic images were analyzed for the percentage of GFP+ dendritic spines with apposed Znt3+ terminals. Ongoing studies involve labeling DGC progenitors with two different RV reporters at different times before or after epileptogenic injury to assess the ages of DGCs that are most likely to be synaptically coupled by mossy fiber inputs onto apical dendrites in the molecular layer, as well as onto hilar basal dendrites.

Results: We found that cells born after pilocarpine-induced SE form about twice as many synapses with mossy fiber terminals compared to cells born 2 or 7 weeks before SE.

Conclusions: These preliminary findings suggest that DGCs born after SE are more likely to form recurrent excitatory circuits than preexisting DGCs.

3.343

MECHANISMS FOR PRENATAL RADIATION-INDUCED RAT CORTICAL MALFORMATIONS THAT SIMULATE CORTICAL DISORGANIZATIONS FOUND IN HUMAN NEUROLOGIC DISORDERS

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Rationale: Malformations of cortical development have been found in epilepsy, Alzheimer's, and learning disabilities. Experiments in rodents have suggested that released reelin controls the positions of pyramidal neurons. For example, Reeler knock-out or mutant reeler mice have neurons with inverted laminations. However, in human neuropathologies of these neurologic disorders, the cortical malformations are not primarily laminar inversions; rather the neurons have abnormal positioning, with oblique and transverse polarities often forming clusters in every layer.In rats radiated for 2 minutes at E17, the prenatal day of greatest numbers of pyramidal cell migrations, tested the hypothesis that the 2 minute interruption in neural stem cell cycling would be significant enough to interfere with normal mature neuron migration and positioning of all types of cerebral neurons. The second hypothesis was that reelin-secreting cells would be disorganized and spatially related to the pyramidal cell clusters.

Methods: 14 dams with age matched pregnancies were given 145 rads at E17 and 7 dams had no radiation for controls. With 10 pups per pregnancy, postnatal (P) developmental comparisons were birth age-matched for 140 radiated pups and 70 control pups for postnatal development at P2, 4, 16, 24, 40 or 90. At these days the radiated and control rats were studied for neuron positions with Cresylviolet (CV), the extracellular matrix protein Reelin (immunofluorescence :IF), and intracellular tubulin Nestin (IF), and at P24, 40, and 60 memory and retention tests (Morris water maze) at P24, 40, and epidural EEG recordings at P60, 90.

Results: Brain tissue sections showed cortical malformations were in neocortex but not in the subcortex. High magnification microscopy and fluoroscopy were necessary to relate neuronal clusters to other proteins. See the figure for comparing CV with adjacent reelin in Control and Radiated. To test the spatial relation of Reelin to mature disorganized neurons (which continued to produce Nestin), adjacent digital images were overlayed and semi-quantified measures were made relating neuron clusters to densest Reelin accumulations. The controls had no neuronal malformations and Reelin was distributed as expected. Post-weaning (P24, 40) learning and retention in the Morris water maze was defective in radiated rats compared to controls. Only in radiated rats did the EEG recordings show epileptiform spikes and mild clinical seizures, never in controls.

Conclusions: In utero radiation at different gestational ages resulted in postnatal neuronal malformations only in the subcortex (E14, 15) or only in the neocortex (E17, 18). Since postmitotic mature neurons are not affected by radiation, the prenatal insults to neural stem cells cycling into mature neurons explains these results. Also, radiation at only E17 showed that Reelin expression was spatially related to the mature but anomalous neocortical neuronal clusters, which all produced heavy molecular weight tubulin(Nestin). Such malformations are comparable to human neurologic disorders.

IMAGE: images/904237_A.jpg

3.344

NEURONAL DEGENERATION IN HYPOTHALAMUS INDUCED BY STATUS EPILEPTICUS IN IMMATURE RATS

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Rationale: Experimental data indicate alteration of hypothalamic functions in animals after severe seizures. It is in agreement with clinical findings in some patients; in many cases their epilepsy started in infancy or early childhood. Therefore we decided to study presence and time course of possible neuronal degeneration induced in hypothalamus of immature rats by status epilepticus.

Methods: Experiments were carried out in Wistar rat pups 12, 15, 18, 21 and 25 days old. SE was induced by pilocarpine (40 mg/kg, i.p.) 24 hours after lithium chloride (3mmol/kg,i.p.) pretreatment. Paraldehyde (0.07-0.3 ml/kg according to age) was administered to interrupt seizures after two hours of continuous convulsions. Control siblings received saline instead of pilocarpine. The rats survived for 4, 8, 12, 24, 48 hours or 1 week after SE. Four to five animals were processed in each survival interval. The animals were perfused with 4 % paraformaldehyde under an overdose of urethane anesthesia. Every fifth coronal section (50 ìm thick) was stained with Fluoro-Jade B (FJB) for detection of degenerating neurons (Schmued and Hopkins 2000), subsequent sections were stained with cresyl violet for differentiation of individual hypothalamic nuclei. Labelled cells were plotted and transferred to standard stereotaxic sections (Paxinos and Watson 2007).

Results: Only isolated degenerating neurons were observed in 12- and 15-day-old animals mainly in the posterior hypothalamus. Since the postnatal day 18 degenerating neurons were distributed in several hypothalamic nuclei. FJB-positive neurons were consistently found in the anterior hypothalamic area, in the ventromedial nucleus, in tuberal area and in the highest number in the mammillary complex. Within the mammillary complex marked neuronal damage was evident in premammillary and supramammillary nuclei. Besides these nuclei, dispersed FJB-positive neurons occured in the lateral hypothalamic area. Animals with SE at the age of 18 and more days exhibited neuronal damage at all survival intervals with a peak at 24 and 48 h after SE. One week after SE persisted degenerating neurons only in the supramammilary nuclei.

Conclusions: Lithium-pilocarpine SE elicited in immature rats led to neuronal degeneration also in the hypothalamus. Consistent neuronal damage was found if SE was induced in 18-day-old and older animals. FJB-positive neurons were found at all survival intervals with a maximum at 24 and 48 h after SE. The degenerating neurons prevailed in the posterior hypothalamic region namely in the mammillary complex.

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3.345

HILAR GABAERGIC INTERNEURONS RECEIVE INCREASED EXCITATORY INPUTS FROM GRANULE CELLS AND PYRAMIDAL NEURONS AFTER TRAUMATIC BRAIN INJURY

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Rationale: Modification of local inhibitory networks in the dentate gyrus may contribute to the development of posttraumatic epilepsy after closed-head brain injury. However, little is known about these potentially pathogenic circuit changes. Enhanced excitatory innervation of dentate GABAergic interneurons has been proposed as a cellular mechanism associated with injury-induced epileptogenesis. We used transgenic mice which express enhanced green fluorescent protein (eGFP) in a subpopulation of somatostatin-positive GABA neurons. We tested whether surviving hilar eGFP neurons received increased excitatory inputs and whether synaptic inhibition of dentate granule cells is altered after experimental brain injury.

Methods: Severe controlled cortical impact injury (1.0 mm impact depth) was administered to 7-8 wk old GIN mice. After 8-13 wks post-injury, coronal slices were prepared for cell attached and whole-cell patch-clamp recordings of hilar eGFP neurons and granule cells. Spontaneous and miniature EPSCs were recorded in eGFP neurons at -60 mV. Spontaneous and miniature IPSCs were recorded in granule cells at 0 mV. Glutamate photostimulation was applied focally to sites along the entire extent of the granule cell layer and in the CA3 region, and responses were examined in hilar eGFP neurons by voltage-clamp recordings. Paired electrical stimulation was applied to the hilus to examine whether a change in presynaptic function of GABAA receptor-mediated feedback inhibition could be detected in granule cells after TBI.

Results: Cell attached and whole-cell voltage-clamp recordings revealed increased action potential and EPSC frequency in hilar GABA neurons from slices ipsilateral to the injury, versus slices contralateral to the injury or from control animals. An increase in evoked excitatory synaptic activity was detected in hilar GABA neurons ipsilateral to the injury after photostimulations applied to both the granule cell and CA3 pyramidal cell layers. Despite increased excitatory synaptic input to inhibitory neurons, whole-cell voltage-clamp recordings in granule cells revealed an overall reduction in spontaneous and miniature IPSC frequency. No change in the probability of GABA release was found in the dentate gyrus after paired electrical stimulation of the hilus.

Conclusions: These findings suggest that excitatory drive to surviving hilar eGFP-positive neurons is enhanced, but synaptic inhibition of granule cells is not restored to control levels after injury. Rewiring patterns of specific inhibitory circuits after brain injury may be an important compensatory mechanism for controlling granule cell excitability in the posttraumatic dentate gyrus.

3.346

PARALLEL COMPUTING ENABLES FULL-SCALE MODELING OF THE CONTROL AND EPILEPTIC RAT DENTATE GYRUS

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Rationale: The dentate gyrus in the adult rat contains over one million neurons. Previously, we published a functional NEURON model of the rat dentate gyrus with over 50,000 biophysically realistic, multicompartmental neurons. With this model, we have studied the roles of network topological changes and highly interconnected “hub cells” in hyperexcitability. However, increases in synaptic conductances and connectivity were required to achieve realistic input to each cell in this 1:20 model. Enlargement of the model up to full size would eliminate these required scaling adjustments, and would represent a major advance in our quest to produce a biologically realistic, data-driven computational model of the rat dentate gyrus.

Methods: To achieve the full-scale model, we rewrote our serial code to be compatible with the recently developed parallel NEURON simulation environment. The synaptic conductances and connectivity were adjusted to remove any scaling factors associated with the 1:20 network, and to allow for congruency with our previously determined structural model of the rat dentate gyrus. Additionally, the original length of the code was reduced by half and each line was documented to improve the accessibility of the model.

Results: The parallel model was able to run on a variable number of processors and was modified to include a load balancing algorithm to ensure efficient use of computational resources. The full-scale model using parallel NEURON has been tested on two different clusters, UCI’s Broadcom Distributed Unified Cluster (BDUC) and TeraGrid’s Ranger Sun Constellation Cluster, providing a near linear speedup of computation time and dramatically increasing the overall memory available to the model.

Conclusions: Through the modification of our model to be compatible with parallel NEURON, we have dramatically increased the computational power available to our model, providing us with the resources to model the full-scale control and epileptic rat dentate gyrus. This increased availability of computational power has also enabled us to incorporate more detail, to approach a more complete model of the dentate gyrus. Currently, we are including more cell types, adding gap junctions, and expanding the model from one to three dimensions.

Through these improvements and model validation tests, we aim to construct a more complete full-scale model of the rat dentate gyrus, to provide a better tool to delineate the role of pathological changes observed in epilepsy on a functional and network level. This work was supported by the NIH (35915 to I.S.)

3.347

SINGLE-CELL MICROINJECTION OF SMALL HYPOTHALAMIC HAMARTOMA NEURONS

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Rationale: Hypothalamic hamartomas (HH) are benign tumors arising in the ventral hypothalamus associated with treatment-resistant epilepsy. HH are intrinsically epileptogenic for gelastic seizures. The basic cellular and molecular mechanisms responsible for seizure genesis are unknown. Recent work has demonstrated that HH neurons are predominately small (<16 ìm), express glutamic acid decarboxylase (GAD), and demonstrate intrinsic pacemaker-like firing in resected tissue slices. These neurons occur in poorly-defined clusters, which are the dominant microarchitectural feature of this pathology, and may represent the functional unit for ictogenesis. The cytology of these neurons has not been previously studied. We sought to link the previously defined electrophysiological features with single cell microanatomy in order to define the dendritic and projection patterns of small HH neurons and to better understand how these cells contribute to functional networks.

Methods: We examined freshly-resected HH tissue from four patients (mean age 11.8 years; 2 females). 350-400 ìm slices were continuously perfused with aCSF and conventional patch-clamp whole-cell microelectrode recordings were conducted under infrared-differential interference contrast microscopy. Electrophysiological data was acquired with a digitizer (DigiData 1322A, Axon Instruments) and analyzed with pClamp 9.1 (Axon Instruments) and Mini Analysis 6 (Synaptosoft). After whole-cell recordings, the neurons were injected with biocytin (Sigma, St. Louis, MO), then stained with 1:1000 Avidin-AF488 (Invitrogen, Carlsbad, CA). Single cell imaging was performed with a Zeiss confocal microscope with z-stacking capabilities. Two-dimensional representations were additionally rendered with the use of a drawing tube.

Results: Fifteen neurons were successfully recorded and injected. The cellular phenotypes were diverse, and a classification for all injected neurons has not yet emerged. One consistent phenotype was identified (n = 5), quite likely representing the small HH neuron, based upon the presence of spontaneous firing with microelectrode recording. The electrophysiological features are noted in the Table. The soma was round or globoid, with maximal diameter in the range of 8 - 23 µm. These cells are bipolar with more extensive processes arising from one end. An axon could not always be identified. Processes, likely axonal, are often very thin (0.1 µm) but could project up to 820 µm away from the soma. Dendritic branches have abundant varicosities, and often demonstrate a corkscrew morphology, but have relatively few spines (Figure).

Conclusions: These results suggest that the relatively simplistic two-neuron model of HH epileptogenesis may need to be refined: cellular morphology in HH tissue is more diverse than previously anticipated, and the spontaneously firing small HH neuron can be larger than described in prior reports. Small HH neurons also have processes that project up to 800 µm from the soma, suggesting that monosynaptic functional networking can include any other neuron within the cluster, but also potentially enable cluster-to-cluster connectivity.

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IMAGE: images/905717_A.jpg

3.348

CELL SPECIFIC ABLATION OF PTEN SIGNALING ALTERS GABAERGIC CIRCUITRY

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Rationale: The PI3 kinase (PI3K) signaling pathway may mediate GABAergic interneuron migration and placement during neocortical development. PTEN is a potent regulatory protein controlling the rate of PI3K signaling through the mTOR pathway in neurons. Previous Cre deletion experiments with a floxed PTEN allele demonstrated neuronal deletion of PTEN led to epilepsy and autistic like behaviors in PTEN CKO mice.

Methods: Classical molecular biological approaches along with cell specific ablation of PTEN signaling was used to test the hypothesis that cell specific PTEN signaling affects formation and function of GABAergic circuitry.

Results: Cell specific ablation of PTEN in excitatory neurons or interneurons led to increased PTZ seizure susceptibility. Subsequent empirical analysis with mice homozygous null for PTEN in GABAergic neurons substantiated our predictions. Notably, deletion of PTEN in interneurons but not excitatory neurons during early development increased the number of interneurons and mRNAs for cell specific GABAergic markers. Deletion of PTEN signaling in either cell type during development regulated the mTOR pathway, providing a plausible explanation for the change in interneuron survival in adult animals.

Conclusions: In conclusion, PTEN expression in developing interneurons is necessary but not sufficient for proper development of GABAergic circuitry. Such signaling pathways may have important implications for patients with the autism/epilepsy phenotype.

3.349

IN VIVO NEUROPROTECTIVE ROLE OF M-TYPE K+ CHANNELS DURING A TRANSIENT ISCHEMIC ATTACK

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Rationale: Voltage-gated K+ channels underlie the basic function of stabilizing a negative membrane potential by counterbalancing the depolarizing effects of Na+ and Ca2+. Voltage-dependent KCNQ family K+ channels, which underlie the M-current, are known to play an important role in controlling neuronal excitability through regulation of action potential firing. KCNQ channels produce slowly activating and deactivating K+ currents with distinct electrophysiological and pharmacological properties. Previous research has shown the physiological importance of maintaining the activity of M-channels and that suppression of M-type K+ channels increases neuronal excitability to levels that provoke epileptic disorders. For example, human KCNQ2

and KCNQ3 channels have been associated with neonatal epilepsy and mutations in these channels have been shown to lead to neonatal convulsions defined by electrical hyperexcitabilty. Since KCNQ channels underlie neuronal excitability, it is of interest to understand if a decrease in membrane excitability has a neuroprotective role, specifically following ischemic insults. Neuronal damage and cell loss is well documented to occur in numerous regions of the brain after transient ischemic attacks (TIAs), thus providing a highly-relevant area of interest.

Methods: The overall hypothesis is that neuroprotection can be enhanced by activating KCNQ channels, thus decreasing the excitability of the neurons directly following TIA. A neuroprotective role can be feasibly studied using a novel therapeutic drug for epilepsy, Retigabine, which has been shown to use a novel mechanism that specifically activates KCNQ2-5 channels and exerts an anticonvulsant profile. To understand the M-currents role during stroke, we used an in vivo living mouse model which permits images of cerebral ischemia within the cortex that is produced using laser-controlled photothrombosis.

Results: Preliminary evidence showed that single vessel photothrombosis successfully caused cell death over a 24-hour period. When Retigabine was injected at the time of the ischemic attack, lesion size was much reduced, as measured by a TTC-staining assay (2,3,5-triphenyltetrazolium chloride) for quantifying the extent of metabolically-impaired tissue.

Conclusions: Thus, this study suggests a strong and exciting model which provides new insights for reducing neuronal damage caused during commonly-occurring ischemic attacks.

3.350

AN INVESTIGATION OF SPONTANEOUS CORTICAL SLOW OSCILLATIONS USING 256-CHANNEL EEG IN NORMAL AND EPILEPTIC PATIENTS

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Rationale: Cortical slow oscillations (CSO) (<1Hz) are generated by the neocortex during non-REM sleep. CSO exist within in-vivo cortical slices and after thalamectomy. These cortical oscillations affect the excitability of neocortical networks with a “down” and “up” state. The “down” state reflects a hyperpolarization and neuronal quiescence of the neocortical cells while the “up” state reflects depolarization and a heightened activity of the neocortical cells. Spike-wave nocturnal seizures have been shown to emerge from CSO (Tucker et. al., 2009). Using dense-array EEG, we attempt to identify the cortical sources for spontaneously generated CSO during slow-wave sleep (SWS) for both normal and epileptic patients.

Methods: We acquired sleep EEG from 14 participants using a 256-channel sensor array (7 normal and 7 epileptic). Sleep stages were identified and CSO were scored during SWS from the first sleep cycle. CSO were evaluated in source space using a 4-shell spherical model that represents the scalp, skull, cerebrospinal fluid, and the cortex with standardized low-resolution brain electromagnetic tomography method (sLORETA). Statistical analyses were performed on the CSO source waveforms.

Results: We found considerable variability between subjects related to CSO source analysis. However, there are shared regions of cortical source activity within medial temporal and medial frontal areas. Evaluation of the cortical source activity within subjects indicated that there are stable regions of activity for different types of CSO.

Conclusions: From these results, we can conclude that the cortex is utilizing the synchronous nature of the CSO “up” and “down” states to regulate different cortical regions during sleep. This may be a way to coordinate neuronal activity such as synaptic plasticity or strengthening during sleep. A better understanding of the modulation of neural excitability in sleep may lead to new options for treatment of nocturnal seizure pathology.

3.351

IN VIVO MODEL OF GROUP I MGLUR-MEDIATED EPILEPTOGENESIS

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Rationale: Evidence from in vitro hippocampal slice studies suggest that group I mGluR stimulation induces epileptogenesis. Furthermore, a group I mGluR-dependent mechanism appears to underlie epilepsy encountered in Fragile X patients (Chung et al., 2005). In this study DHPG, a group I mGluR agonist was infused into the lateral ventricle of the rat to determine whether this epileptogenic process can occur in normal wild-type animals.

Methods: Adult male Sprague-Dawley rats (275-325g; n= 6) were anesthetized with isoflurane. Each rat was placed in a stereotaxic apparatus, the skull surface exposed and a hole was drilled to allow for drug infusion. A needle attached to a Hamilton syringe was lowered into the lateral ventricle at the following coordinates measured from bregma: A-P -0.8mm, M-L +1.5mm, D-V 4.2mm from skull surface. DHPG dissolved in saline (50mM, 2ul) was infused over 40min and the needle was left in place for an additional 10min. The wound was closed and the rat was allowed to recover. Behavior was monitored continuously for 5hr after infusion. Each animal was also observed for limited periods over the next 48hr. Control rats (n=3) were treated in a similar manner except they received a saline infusion.

Results: All rats recovered from anesthesia within 20min. The experimental animals exhibited the following behaviors: face washing, backwards walking, prolonged episodes of wet dog shakes (WDS; n=6/6), prolonged staring episodes (SE; n=6/6) and limbic seizures (n=1/6). DHPG-treated rats exhibited a significant increase in the mean (±SEM) number of SE (10.33±2.12 vs 0.33±0.33, $p<0.02$). The maximum duration of the SE ranged from 9-25min. There was also a significant increase in the mean number of WDS episodes (23.5±5.56 vs 2.33±1.2; $p<0.04$) in the DHPG-treated rats. Twenty-four to 48hr after drug infusion multiple WDS and seizures were observed. Control animals exhibited a limited number of post surgery WDS but spent the majority of the observation period sleeping.

Conclusions: These results provide evidence that activation of group I mGluR receptors induced recurrent seizure and sub-seizure epileptic activities long after receptor activation. The observation indicates that group I mGluR stimulation constitutes a broadly relevant epileptogenic process. Since DHPG was infused into the ventricle its direct site of action is unknown. However the observation of pronounced wet dog shake activity suggests a hippocampal origin and site of action.

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EARLY-ONSET SEIZURES IN ADULT MICE FOLLOWING HYPOXIC-ISCHEMIC BRAIN INJURY

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Rationale: Stroke is a major cause of seizures and epilepsy in adult-aging populations, and the pathophysiology behind post-stroke seizures is presently unclear. Experimental studies in animal models are of great value to improve our knowledge in this field. However, systematic investigations of post-stroke seizures/epilepsy in adult animals remain limited. The aim of our present study is to explore whether hypoxic-ischemic (HI) brain injury in adult mice serves a useful model to examine post-stroke seizures.

Methods: C57 black mice of 3-9 months were used in the present experiments. Mice received a permanent, unilateral occlusion of right common carotid artery under isoflurane anaesthesia (2%). About one hour later while recovered from anaesthesia, the animals were challenged with global hypoxia via exposing to 8% oxygen for 30 min in an airtight chamber. After the hypoxic episode, the animals underwent continuous video monitoring. Intra-cranial EEG recordings were conducted in some experiments, and the EEG activities of the right hippocampus and left neocortex (ipsilateral and contralateral to carotid occlusion respectively) were monitored during and after HI. The severity of post-HI convulsions was quantified using a generalized seizure score system as per Pohl and Mares (1987) and Veliskova et al. (1990). Sham control mice were similarly operated but without the carotid artery occlusion and global hypoxia. After in vivo experiments, the animals were later sacrificed for histological assessment or for electrophysiological recordings in brain slices.

Results: Severe seizures were observed in about 30% of mice examined following the HI insults. These seizures occurred largely within 12-36 hours post-HI and manifested fast running and jumping, barrel rolling, falling with the loss of righting reflex. Histological examination revealed that the hippocampus and temporal cortex ipsilateral to the carotid artery occlusion were grossly damaged. In contrast, such ipsilateral brain damage was absent in mice that did not exhibit severe behavioural seizures.

Conclusions: It appears to be a notable correlation between the severity of HI-induced ipsilateral brain injury and the occurrence of post-HI seizures. Works are in progress to characterize EEG activities in post-HI mice and to examine the effects of anticonvulsive agents on post-HI seizures.

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HIGH-FREQUENCY (80-500 HZ) OSCILLATIONS IN A RAT MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: High-frequency oscillations (HFOs) (80-500 Hz) are recorded in mesial temporal regions of epileptic patients as well as in animal models of temporal lobe epilepsy (TLE). They are mostly related to interictal spikes, occur more frequently during periods of slow-wave sleep, and may reflect seizure onset zones. However, the spatial and temporal characteristics of HFOs following the initial status epilepticus (SE) are poorly defined. In this study, we have addressed the developmental pattern of HFOs in the pilocarpine model of TLE and performed continuous in vivo recordings in parahippocampal regions and in the hippocampus following SE.

Methods: Seven rats were implanted with bipolar depth electrodes aimed at the dentate gyrus, CA3 region, subiculum and entorhinal cortex, 3 days after an initial pilocarpine-induced SE (380 mg/kg, i.p.). Local field potential (LFP) recordings were then performed on a 24-hr basis, from the 4th to the 15th day after SE.

Ten minutes slow-wave sleep periods were selected for analysis. Raw LFP recordings were band-pass filtered and then normalized. Peaks that crossed a standard threshold (3 SD) for at least 3 consecutive cycles were kept for analysis. Rates (number of events/day) of interictal spikes without HFOs or co-occurring with fast ripples and with ripples were calculated.

Results: The first spontaneous seizure occurred after a mean latency of 6.1 ± 2.5 (SD) days from SE. Seizures (duration : 77.4 ± 35.2 s, n = 155) were observed in every rat and were characterised by a cluster occurring between the 9th and the 12th day after SE. Different developmental patterns of interictal spike rates (n = 12,886) were observed depending on the co-occurrence with HFOs. Rates of interictal spikes without HFOs (74.4 ± 4.4 % of all recorded interictal spikes) increased in every regions when seizure rates were low. On the contrary, rates of interictal spikes with fast ripples (4.9 ±4.6 %) first increased in parahippocampal regions and when seizure rates were low, but increased in the hippocampus only when seizure rates were high (between the 9th and 12th day of recording). Interictal spikes with ripples (9.0 ±3.6 %) showed a similar developmental pattern, but relation to seizure occurrence was less specific than when considering interictal spikes with fast ripples. Rates of interictal spikes with ripples also significantly decreased over time in the hippocampus ($r2 = -0.66$, $p < 0.05$) and in the entorhinal cortex ($r2 = -0.67$, $p < 0.05$), suggesting that they may be replaced over time by fast ripples in some regions.

Conclusions: Interictal spikes may point to different dynamic processes that underlie epileptogenesis, depending on their co-occurrence with HFOs. Rates of interictal spikes with fast ripples showed a better relation with seizure occurrence and we observed different patterns of evolution depending on the region in which they were recorded. These results thus suggest that interictal spikes with fast ripples reflect a dynamic pathological process that first involves parahippocampal structures and that progressively brings the hippocampus close to seizure occurrence.

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CORTICAL AND SUBCORTICAL NETWORK DYSFUNCTION IN LIMBIC SEIZURES: HIGH FIELD BOLD FMRI IN A RODENT COMPLEX PARTIAL SEIZURE MODEL

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Rationale: Temporal lobe epilepsy is marked by focal seizures which are either complex, characterized by deficits in consciousness, or simple, involving no loss of consciousness. However, it is not understood how a seizure confined to the temporal lobe could cause loss of consciousness. In humans, complex partial seizures with loss of consciousness are characterized by slow waves across the neocortex concurrent with polyspike seizure activity in the temporal lobe. We have previously investigated a rodent model of hippocampal-stimulated seizures utilizing a single radio frequency surface coil to map dorsal brain structures involved in limbic seizures. The imaging data from the more ventral subcortical structures—which may be crucial mechanistically for neocortical slow activity— were limited by decreased signal-to-noise ratio (SNR).

Methods: To obtain images with dramatically increased SNR in more ventral structures, we developed a new 2x1 quadrature coil, which acts as a transreciever. Using our newly developed coil, blood oxygen level dependent (BOLD) fMRI measurements were performed on a 9.4T system during seizures induced by brief hippocampal stimulation with a bipolar tungsten electrode.

Results: FMRI increases were seen in the hippocampus, septal nuclei, anterior hypothalamus and mediodorsal thalamus. FMRI decreases were seen in cortical regions including the orbital frontal, cingulate and retrosplenial cortex, as well as in other neocortical areas to a lesser degree. FMRI decreases were also observed in subcortical regions such as the thalamic intralaminar and posterior nuclei, basal ganglia, and midbrain tegmentum.

Conclusions: Together, these imaging findings suggest a possible mechanism for ictal neocortical slowing based on 3 overlapping networks. (1) Hippocampal seizures propagate to the structures of the limbic system such as the mediodorsal thalamus, anterior hypothalamus and septal nuclei, (2) inhibitory projections of the lateral septum, anterior hypothalamus or other regions suppress the forebrain arousal systems and (3) neuronal activity in central thalamic nuclei and the brainstem reticular formation are decreased which removes excitatory input to the neocortex. These new subcortical imaging data suggest new and potentially crucial nodes of the network responsible for neocortical dysfunction and impaired consciousness in temporal lobe seizures as well as provide targets for mechanistic studies in the future.

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EFFECT OF BETA-ESTRADIOL ON SYNAPTIC PLASTICITY IN DENTATE GYRUS DEPENDS ON STIMULATION PARADIGM

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Rationale: Estrogens differentially regulate neuronal excitability, synaptic plasticity, as well as biphasically modulate seizure activity: Some types of seizures may be exacerbated while other types are rather attenuated by estrogens. The mechanisms involved in these distinct effects of estrogens on seizure activity are unknown. Here we examined a form of synaptic plasticity in the dentate gyrus that may share some mechanisms with seizures.

The dentate gyrus is a part of hippocampal formation and receives its main inputs from the entorhinal cortex via the perforant pathway; it serves as a gate and filters incoming information and seizure activity into the hippocampus. Previously we have reported that administration of beta-estradiol (EB) in ovariectomized (OVX) rats persistently enhances inhibition of dentate granule cells by selectively filtering out incoming low-frequency (3-5 Hz) but not the high-frequency activities. Using long-term potentiation (LTP) we investigated the effects of EB on synaptic plasticity in the dentate gyrus using different frequency induction paradigms.

Methods: Adult female Sprague - Dawley rats were OVX and following one week treated subcutaneously with EB (2 ìg/0.1 ml) or oil (0.1 ml) daily for 4 days. Transversal slices containing the entorhinal cortex-hippocampus were prepared for extracellular recording. Our LTP induction paradigms involved (1) A theta burst stimulation (TBS), (2) Standard high-frequency stimulation (sHFS) and (3) Repeated high-frequency stimulation (rHFS).

Results: In slices from EB-treated rats, the TBS of medial perforant pathway elicited smaller LTP compared to slices from oil-injected OVX controls. On the other hand, rHFS of medial perforant pathway in slices from EB-treated rats induced more robust LTP than that in oil-injected OVX controls. The magnitude of LTP induced by sHFS of medial perforant pathway didn't differ between EB and oil treated rats.

Conclusions: Our data suggest that the anticonvulsant or proconvulsant effects of beta-estradiol in epileptic patients may depend on frequencies involved in seizure activity in distinct types of epilepsy.

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EARLY ENHANCEMENT OF PHASIC GABAERGIC INHIBITION IN THE PILOCARPINE-TREATED RAT SUBICULUM

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Rationale: Temporal lobe epilepsy (TLE) is the most common type of partial complex epilepsy, and involves the hippocampus, parahippocampal regions and the temporal neocortex. Among these, the subiculum is of particular interest for TLE pathogenesis due to its powerful GABAergic inhibition, which endows this region with a gating role of hippocampal outputs (Benini and Avoli. J Physiol 566:885-900, 2005). Notably, in epileptic tissue, the subiculum appears to reinforce ictal-like synchronization (Panuccio et al. Neurobiol Dis, 2010. doi:10.1016/j.nbd.2010.05.003). Although the implication of GABAergic inhibition in TLE pathogenesis has been evidenced by several studies, none of these has focused on the changes occurring in the subiculum following an epileptogenic insult before the establishment of TLE (latent period). Here, we analyzed spontaneous $GABA_A$-mediated inhibitory post-synaptic currents ($GABA_A$-sIPSCs) generated by subicular neurons in pilocarpine-treated and non-epileptic control (NEC) tissue.

Methods: Horizontal brain slices 300 ìm thick were obtained from male, adult Sprague-Dawley rats, 3-6 days after either pilocarpine-induced status epilepticus (SE) lasting 2 hours or after sham injection. Whole-cell patch-clamp recordings of pharmacologically isolated $GABA_A$-sIPSCs were performed from visually identified subicular principal neurons in symmetric chloride condition at a holding potential of -70 mV. Data were compared with the unpaired t-test and considered significantly different if $p<0.05$. Values are expressed as mean±SEM.

Results: Subicular neurons of pilocarpine-treated animals generated $GABA_A$-sIPSCs which occurred at rates similar to those in NEC tissue (mean interval - NEC: 0.84±0.35 s, n= 18; pilocarpine: 0.73±0.22 s, n= 12). Moreover, current density was similar in NEC (4.34±0.66 pA/pF, n= 18) and pilocarpine-treated subicular neurons (4.96±0.59 pA/pF, n= 12). However, $GABA_A$-sIPSCs generated by the latter cells were characterized by a significantly slower decay time constant (NEC: 6.87±0.57 ms, n= 18; pilocarpine: 10.86±1.51 ms, n= 12; p= 0.006), a larger charge transfer, Q/Cm (NEC: 26.32±3.76 pA*ms/pF, n= 18; pilocarpine: 56.11±13.21 pA*ms/pF, n= 12; p= 0.012), and a prolonged half-width (NEC: 4.24±0.44 ms, n= 18; pilocarpine: 7.27±1.34 ms, n= 12; p= 0.015). Overall, these changes in current kinetics resulted in a significant increase of the average total current, calculated as Q/Cm*IPSCs frequency (NEC: 0.11±0.03 pA, n= 18; pilocarpine: 0.23±0.09 pA, n= 12; p<0.001).

Conclusions: Generation of $GABA_A$-sIPSCs is not impaired in subicular principal neurons following pilocarpine-induced SE. However, in spite of no apparent change in current density and sIPSCs frequency, a paradoxical enhancement of the average total current is brought about by the slower current kinetics. We propose that this phenomenon represents an early compensatory mechanism to counteract the documented interneuron loss, which would otherwise allow the spread of excitation from the hippocampus proper to parahippocampal areas.

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TEMPORAL LOBE EPILEPSY INDUCED INCREASES IN PERSISTENT (INAP) AND RESURGENT (INAR) NA CURRENTS

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Rationale: Temporal lobe epilepsy (TLE) is a common form of adult epilepsy involving the limbic structures of the temporal lobe. Layer II neurons of the entorhinal cortex (EC) form the major excitatory input into the hippocampus via the perforant path and consist of non-stellate and stellate neurons. These neurons are spared and hyper-excitable in TLE. Since sodium (Na) channels play a critical role in action potential (AP) generation and conduction we sought to determine if Na channel gating parameters and expression levels were altered in TLE. Specifically we focused on persistent (INaP) and resurgent (INaR) Na currents since these two currents arise mainly from activation of the Nav1.6 Na channel isoform and are major contributors to the generation of AP bursts.

Methods: Brain slices were prepared from control rats and rats with TLE. INaP and INaR currents were recorded from visually identified EC layer II non-stellate and stellate neurons.

Results: Both TLE stellate and non-stellate neurons had larger INaP current amplitudes when compared to control neurons. In non-stellate neurons control INaP currents had an amplitude of -121.3 ± 26.1 pA (n = 9) and were significantly (P<0.01) increased in TLE to -358 ± 46.2 pA (n = 7). In a similar manner, TLE stellate neurons also had increased INaP current amplitudes. Amplitudes were increased from -153.5 ±18.9 pA (n = 9) under control conditions to -356.8 ± 31.7 pA (n = 7: P < 0.01) in TLE.

INaR current amplitudes were also increased in TLE. INaR currents in non-stellate neurons were profoundly increased from -514.8 ± 72.4 pA (n = 6) in control to -1394.6 ± 82.1 pA (n = 7: P < 0.001) in TLE. INaR currents in stellate neurons were also significantly larger in TLE compared to controls. Control amplitudes were increased from -568.9 ± 58.9 pA (n = 7) to -1477.8 ± 75.2 pA (n = 7: P < 0.001) in TLE. Families of INaR currents were evoked to construct current voltage plots. TLE non-stellate neurons had significantly (P<0.05) hyperpolarized INaR V1/2 values (-61.3 ± 1.9; n=7 in control compared with -68.0 ± 2.3; n=8 in TLE). Slopes were also slowed in TLE (-5.0 ± 0.6 in control compared with -6.2 ± 0.5 in TLE). In contrast to non-stellate neurons, INaR V1/2 values in stellate neurons were unchanged (-70.1 ± 2.8; n=10: in control compared with -65.4 ± 2.9; n=6 in TLE). Slope values were slowed in TLE (-4.0 ± 0.4 in control compared with -7.0 ± 0.4 in TLE; P<0.05). Immunohistochemistry experiments revealed increased staining intensity of Nav1.6 along the axon initial segment (AIS) in TLE brain slices when compared to control.

Conclusions: We propose that increases in INaR and INaP in TLE may contribute to the generation of AP bursts previously reported in EC layer II neurons in TLE, leading to seizure generation and spread within the limbic system.

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MRI HIPPOCAMPAL VOLUME IS ASSOCIATED WITH CA1 NEURON DENSITY AND CHONDROITIN SULFATE EXPRESSION IN TEMPORAL LOBE EPILEPSY

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Rationale: Mesial temporal lobe epilepsy (MTLE) is often associated with poor seizure control. Hippocampal sclerosis is a common pathological finding in MTLE and is characterized by neuron loss and gliosis, which is particularly severe in the CA1 and prosubiculum subfields. Gliosis can increase extracellular matrix (ECM) production, affecting water homeostasis and extracellular space volume. Hyaluronan (HA) and chondroitin sulfate (CS), the main ECM molecules, are increased in MTLE patients. Aquaporin 4 (AQP4), a water channel found in astrocytes, is also altered on MTLE and can affect oedema generation and draining. Although studies have indicated association between CA1 neuron density and MRI hippocampal volume, the relative contribution of other tissue elements in the hippocampal volume has not been evaluated. Our aim was to evaluate the role of hippocampal neuron and glial populations, and molecules associated with water homeostasis in MTLE patients with different MRI hippocampal volumes.

Methods: Patients with MTLE (n=69) were evaluated for MRI volumetry; and hippocampal histological sections from surgical biopsies and from autopsy patients without history and evidence of brain pathology (n=20) were processed for immunohistochemistry for NeuN, GFAP, HLA-DR, AQP4, CS-56 and histochemistry for HA. Neuronal population (neurons/mm3) was evaluated by cell count and all immunohistochemistry were evaluated by immunoreactive area (im2). HA histochemistry was evaluated by gray level.

Results: Hippocampal volumes in MTLE patients were of 2.314±0.063 cm3 (mean±SEM), ranging from 1.338 to 3.704 cm3. Compared to control, MTLE showed lower neuronal density (Control = 41,853, MTLE = 4,484; Mann-Whitney, median, p<0.001), lower immunopositive areas for NeuN (Control = 474, MTLE = 55; p<0.001), perivascular AQP4 (Control = 179, MTLE = 85; p=0.001) and higher immunopositive areas of GFAP (Control = 52, MTLE =

2185; p<0.001), HLA-DR (Control = 11, MTLE = 62; p<0.001) and CS-56 (Control = 81, MTLE = 267; p=0.003). Positive correlations were found between hippocampal volume and neuronal density (r=0.405; p<0.001), hippocampal volume and immunoreactive areas for NeuN (r=0.451; p<0.001) and for CS-56 (r=0.295; p=0.024). Multiple linear regression models revealed, respectively, predictions of 37% (p<0.001) and 36% (p<0.001) of hippocampal volume for the combinations between immunoreactive areas of NeuN and CS-56 [Hippocampal Volume = 2.067 + (0.00182 * CA1 NeuN area) + (0.000334 * CA1 CS-56 area)] and of neuronal density and immunoreactive area for CS-56 [Hippocampal Volume = 2.050 + (0.0309 * CA1 neuronal density) + (0.000343 * CA1 CS-56 area)].

Conclusions: Hippocampal volume in MTLE is partially explained by neuronal population and extracellular matrix chondroitin sulfate quantity.

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IS BGT1 MRNA EXPRESSION FOLLOWING STATUS EPILEPTICUS INFLUENCED BY INFLAMMATION AND/OR DEHYDRATION IN C57/B6 MICE?

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Rationale: Alterations in the mRNA expression of GABA transporters (GATs) 1 and 3, and the osmolyte transporter sodium-myoinositol co-transporter (SMIT) have been shown to occur in epilepsy and seizure models. However, the influence of seizure activity on expression of the betaine/GABA transporter, BGT1, is unknown. BGT1 may be susceptible to regulation similar to other osmolyte-related genes, other GABA transporters, or both. Therefore, this study compared the expression of BGT1 to that of osmolyte-related genes SMIT, taurine transporter (TauT), aldose reductase (AR), and GATs 1 and 3 following status epilepticus (SE). The possible contributory role of dehydration or an inflammatory insult on gene expression was also investigated.

Methods: Pilocarpine status was induced in male C57/B6 mice. Hippocampi were collected for gene expression determinations at 8 hours (h), 24 h, 72 h, one week, and four weeks post-SE. Hippocampal mRNA levels from SE animals were compared to those from hippocampi obtained from animals experiencing either an inflammatory insult (LPS, 4 mg/kg, i.p.) or 24 h water withdrawal to determine if either inflammation or dehydration could contribute to the results observed post-SE.

Results: Twenty-four hours post-SE, BGT1, SMIT, and TauT mRNA expression were significantly increased. At the 72 h and 4-week time-points, BGT1, GAT1, and GAT 3 were significantly decreased. Hence, the expression of BGT1 switched from being similar to that of the osmolyte transporters at an early time-point to being more like the GABA transporters. Following SE, animals are dehydrated to a similar extent to animals that have had water withheld for 24 hours. However, the mRNA values for BGT1, TauT, and SMIT following 24-hour water withdrawal were significantly lower than the values obtained following SE. This result suggests that dehydration does not fully account for the upregulation of the osmolyte transporters following SE. Following an inflammatory insult, GAT1 and GAT3 values were not significantly different from SE animals, supporting the hypothesis that inflammation may contribute to GAT downregulation post-SE. BGT1 values, however, showed a significantly smaller decrease following LPS compared to that seen post-SE, which suggests that inflammation does not significantly contribute to the downregulation of this transporter post-SE.

Conclusions: Neither plasma osmolality nor inflammation appear to fully account for the changes seen in BGT1 mRNA expression post-SE. The mediator(s) of BGT1 mRNA regulation in the brain remain(s) undetermined.

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GALANIN RECEPTOR TYPE 1 DELETION EXACERBATES HIPPOCAMPAL NEURONAL LOSS AFTER SYSTEMIC KAINATE ADMINISTRATION IN MICE

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Rationale: Inbred strains of mice differ in their susceptibility to excitotoxin-induced cell death, but the genetic basis of individual variation is unknown. Previous studies using quantitative trait loci (QTL) mapping established that the distal region of mouse chromosome 18 [*Sicd1*] contains a gene(s) that is probably responsible for the difference in seizure-induced cell death susceptibility between two inbred strains, C57BL/6J and FVB/NJ. Previous studies have identified galanin receptor type 1 (GalR1) as a compelling candidate gene for this locus based on expression analysis (Kong et al., 2008) and its known role as a neuroprotective factor for the hippocampus. Thus, we wanted to examine the role of GalR1 in modulating seizure-induced excitotoxic cell death by utilizing GalR1 null mutant mice.

Methods: GalR1$^{-/-}$ mice were originally provided by Delta Lexicon and purchased from Jackson Laboratories. The mice were all first generation offspring resulting from the mating of C57BL/6JGalR1$^{+/-}$ females (N10-12) to C57BL/6JGalR1$^{+/-}$ males (N11-13). Young adult (GalR$^{1+/+}$, GalR1$^{-/-}$, and C57BL/6J) mice received one subcutaneous injection of kainic acid (KA; Nanocs, NY). Following KA injections, mice were monitored continuously for 4 h for the onset of locomotor activity, behavioral manifestations of limbic seizure episodes, and scored for seizure activity as defined previously (Racine, 1972). Brains from animals in each age group were processed for light microscopic histopathologic evaluation seven days following kainate administration to evaluate the severity of seizure-induced brain damage.

Results: Neither latency to onset of severe seizures nor duration of severe seizures was modulated by GalR1 genotype. However, GalR1$^{-/-}$ mice showed increased susceptibility to seizure-induced cell death as compared to GalR1 wildtype mice. In particular, while KA administration into GalR1$^{+/+}$ mice generated no degeneration, KA administration into GalR1$^{-/-}$ mice generated pronounced (2-fold) loss in areas CA3 and CA1 of the hippocampal formation. Similarly, we found a substantial increase in the extent of neuronal damage throughout the hippocampus of normally excitotoxin cell death-resistant mice (C57BL/6J) that received intra-hippocampal administration of the GalR1 antagonist, galantide, prior to kainate administration, as compared to those mice administered saline prior to kainate administration.

Conclusions: Our results found that a reduction of GalR1 expression in the C57BL/6J mouse renders them susceptible to excitotoxic injury following systemic kainate administration. As well, we found a substantial increase in the extent of neuronal damage throughout the hippocampus of normally excitotoxic cell death-resistant mice (C57BL/6J) that received intra-hippocampal administration of the GalR1 antagonist prior to kainate administration. These results lend further

support for the hypothesis that GalR1 can elicit a seizure-induced cell death susceptible phenotype.

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TEMPORAL CYTOKINE EXPRESSION PATTERNS IN THE RAT HIPPOCAMPUS FOLLOWING A TRAUMATIC BRAIN INJURY

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Rationale: In the united states, traumatic brain injury (TBI) occurs in about 2 million people annually, not including the high incidence rates amongst our military personnel. Considering the often devastating outcomes, including post-traumatic epilepsy, understanding the primary and secondary mechanisms involved in TBI is essential. TBI can be studied using various types of animal models that include: lateral fluid percussion injury, controlled cortical impact and impact acceleration injury, including the weight drop method. In these models, pro and anti-inflammatory cytokines are altered after TBI and these inflammatory changes may be related to the primary and secondary symptoms that include edema, cell death and cognitive impairments. Considering that diagnostic tools for the severity and persistence of TBI is lacking, it is important to define the temporal expression patterns of inflammatory proteins in specific regions of the brain following TBI. Although there is a growing literature on this topic, there are significant gaps in the literature. In addition, it is possible that different animal models of TBI produce differential inflammatory profiles. Understanding commonalities between these models might provide further insight into the treatment of brain trauma and the prevention of post-traumatic epilepsy. Therefore, the aim of this study was to characterize the acute biochemical changes of multiple inflammatory cytokines in the rat hippocampus following an impact acceleration injury.

Methods: Male Sprague-Dawley rats (200-250gms) were subjected to TBI using a weight-drop version of an impact acceleration injury. A separate group of sham rats served as controls. At 6 or 24 hrs after TBI, animals were euthanized, followed by rapid dissection of the hippocampus. Immediately after extraction, the hippocampus was analyzed for IL-1beta, IL-2, IFN-gamma, GMCSF, VEGF and TNF-alpha using the Luminex system.

Results: The results show that in the hippocampus, IL-1beta was significantly decreased between 6 and 24 hr following TBI, whereas TNF-alpha was elevated in TBI rats at 6 hrs after TBI. However, at 24 hours after injury, TNF-alpha was significantly decreased in TBI rats compared to controls. VEGF was also decreased in TBI rats when compared to controls at 24 hr. The data also show a significant increase of IL-2, IFN-gamma and GMCSF between 6 and 24 hrs following TBI. The results suggest that 6 hrs after TBI there is an increased synthesis of the pro-inflammatory TNF-alpha , IFN-gamma and GMCSF which is sustained even after 24 hr. Interestingly, TNF-alpha was significantly decreased in TBI rats compared to controls at the 24 hr timepoint.

Conclusions: TBI is a leading cause of epilepsy with a known etiology. Inflammatory signals may be involved in mediating the increased seizure susceptibility that is seen following TBI. The current data add to our growing understanding of the patterns of pro- and anti-inflammatory cytokine expression following TBI.

3.362

MTOR CASCADE ACTIVATION OBSERVED IN HUMAN HIPPOCAMPAL SCLEROSIS IS NOT RECAPITULATED IN A RAT PILOCARPINE MODEL OF EPILEPSY

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Rationale: Previously we have shown that scar astrocytes found in hippocampal sclerosis (HS) in MTLE revealed increased phosphorylation of ribosomal protein S6 (pS6) (Mikell et al., 2009). In order to elucidate mechanisms of mTOR cascade activation in HS, we studied mTOR cascade in the development of the gliotic scar emerging after neuronal loss in a pilocarpine model of epilepsy in rats.

Methods: We used immunohistochemistry and western blotting to evaluate levels of phosphorylated and non-phosphorylated downstream components of mTOR, p70 S6K, S6 and 4EB-P1, in a pilocarpine-induced model of epilepsy in rats and in surgically resected hippocampi in patients with medically intractable MTLE.

Results: Two brain areas in pilocarpine treated rats usually revealed severe neuronal damage and accompanying astrogliosis: hippocampus and piriform/entorhinal cortex. In the first two weeks after insult, reactive astrocytes bordering the damaged areas expressed high levels of pS6. In one month after insult, only a few astrocytes bordering this area were pS6 immunopositive. Later on, when the glial scar began to form, gliotic astrocytes did not show activation of mTOR pathway. Thus in 3, 6 months and in 1.2 years (the latest time studied) scar astrocytes did not show mTOR activation and only some neurons were pS6 immunopositive. In all studied cases of human HS, scar astrocytes revealed high levels of pS6 and 4EB-P1.

Conclusions: Based on the known data about the kinetics of mTOR activation, we argue that HS in surgically resected cases of MTLE is not a static phenomenon finalizing neuronal demise. In contrast to the traditional gliotic scar, in HS, there are some ongoing cellular processes that result in mTOR pathway activity.

3.363

MECHANISMS GENERATING SPIKE-WAVE DISCHARGES IN A DETAILED THALAMOCORTICAL SIMULATION

Evan A. Thomas[1], J. D. Chambers[2], S. Petrou[1], D. Abramson[3] and S. F. Berkovic[4] ([1]Centre for Neuroscience, University of Melbourne, Parkville, VIC, Australia; [2]Howard Florey Institute, Parkville, VIC, Australia; [3]Faculty of Information Technology, Monash University, Caulfield, VIC, Australia and [4]Department of Medicine, Austin Health, University of Melbourne, Heidelberg West, VIC, Australia)

Rationale: Absence seizures are possibly the best understood seizure type, due in large part to the excellent rodent models available. However the frequency of spike and wave discharge (SWD) in rodent models is 5-8Hz while in human it is around 3Hz. This raises concerns about the relevance of animal models to the human condition. Given the lack of a 3Hz animal model an alternative approach to understanding this frequency difference is to build biophysically detailed mathematical models of neural circuits that can then be simulated on computers. These models can be explored in ways that are impossible in the wet

lab leading to the development of testable hypotheses. To link molecular level biophysics to large network dynamics, these models must necessarily be complex themselves thus requiring considerable computer resources to fully explore their potential.

Methods: Our simulation is based on a previously published highly detailed model of a thalamocortical column (Traub, et al 2005). This model has been ported to the NEURON simulation environment and modified to run in parallel over large numbers of processors (code provided by M Hines). The code runs efficiently with up to 40 processors and takes 30-40 processor hours to simulate 1s of network time. We updated the model to include recently published anatomical data. The model realistically describes the electrophysiological and anatomical properties of important cells in the thalamocortical circuits of a single column. Cells modelled include principal cells in Layers 2/3, 3, 5, and 6, inhibitory interneurons in Layers 2/3 and 6, nucleus reticularis cells and thalamocortical relay cells. Model neurons have realistic morphology and membrane distribution of voltage and calcium gated conductances. GABA, AMPA and NMDA synapses were also modelled. We used Nimrod, a specialised parametric modelling system, to perform a fractional factorial parameter space search, a method by which only a fraction of all possible parameter combinations are evaluated. Approximately 30 parameters describing the magnitude of synaptic conductances and the strength of exogenous inputs were examined.

Results: To represent sensory input, current injections were played into thalamocortical relay cells. To represent transcolumnar input, current injections were played into later 2/3 pyramidal cells and/or layer 5 pyramidal cells. From different combinations of three types of inputs, a range of behaviours were observed from high frequency gamma-like oscillations to oscillations with SWD-like frequencies. In states where low frequency oscillations were observed, increasing the current injections into layer 5 pyramidal cells could alter the frequency from 2 Hz to 8 Hz. Altering the relative levels of excitatory transmission (AMPA and NMDA) and inhibitory transmission (GABA) could also produce a large range of network behaviours for a given input.

Conclusions: Different frequency of SWD observed between humans and rodents may be explained by different levels of input from nearby cortical columns during a seizure.

3.364

INCREASED ENDOPLASMIC RETICULUM STRESS IN THE AMYGDALOID KINDLING MODEL OF RATS

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Rationale: Endoplasmic Reticulum (ER) is an organelle responsible for correct folding and sorting of proteins contributing to neurogenesis and neuronal cell death. We used rapid kindling to analyze specific ER stress marker expression underlying focal epileptogenesis and to correlate ER stress and neuronal apoptotic changes.

Methods: Seven-weeks-old rats in 3 groups: sham (n=6), partial kindled rats (n=8), and over-kindled rats (n=9). Over kindled rats received over100 stimuli. Partial kindled animals had stimuli halted at Stage 2. Protein from ipsilateral hippocampus was electrophoresed on SDS-PAGE, followed by hybridized with primary antibodies, anti-KDEL, Bcl-2, BDNF, CHOP, NMDA-R1 &2A, GluR1, and â-tubulin.

Results: Western blotting revealed that the ER stress marker BiP was markedly increased in both partial- and over-kindled groups. BiP expression was 9-fold greater than control in partial-kindling while 2-fold greater than control in over-kindled animals. Although ER stress response was accelerated, CHOP expression, which up-regulates when apoptosis signaling is accelerated by ER stress, was suppressed. Bcl-2, which acts as an anti-apoptotic molecule, was up-regulated in the over-kindled group.

Conclusions: Remarkable elevation of BiP was found in partial kindled animals, but not in over-kindled. Elevation of markers of ER stress in partial seizures might reflect transfer of discharge to contralateral limbic structures. We observed functional changes and neurogenesis in limbic structure during kindling. Wide-spread functional changes in several membrane and secreted proteins, including NMDA-R1&R2A and BDNF, for mossy fiber re-construction on CA3 area, that are related to protein synthesis in ER, may be of importance in epileptogenesis.

3.365

IMMATURE LARGE NEWBORN NEURONS IN HUMAN HIPPOCAMPAL DENTATE GYRUS FROM PATIENTS WITH TEMPORAL LOBE EPILEPSY

Hidenori Sugano, M. Nakajima, H. Okura, T. Higo and H. Arai (Juntendo University, School of Medicine, Tokyo, Japan)

Rationale: The aim of this study is to evaluate the maturation of the newborn neuron in the hippocampal dentate gyrus using human specimens from the patients with temporal lobe epilepsy.

Methods: Human hippocampal specimens were obtained at surgery for temporal lobe epilepsy and divided into two groups: with or without hippocampal sclerosis (HS). We stained them for newborn neurons by PSA-NCAM, and counted positive cells in the subgranular cell layer (SGCL) and hilus. We also stained for Hu, Doublecortine (DCX), NeuroD, NeuN with PSA-NCAM to analyze the maturation of these newborn neurons. We also used NKCC1 and KCC2 stains to demonstrate the maturation of ion-transporters.

Results: More PSA-NCAM positive neurons were seen in the group without HS than with HS. Size of the newborn neurons in the group without HS was the same as the mature granular cell. However, 38.4% out of all newborn neurons in the HS group were large cells more than 30ìm. From the large newborn neurons population, 79.5% were located in the hilus, and more than 80% stained with Hu, NeuroD, and NeuN. The percentages of DCX and KCC2 positive large neurons in the group with HS were less than those of the group without HS. The percentages of NeuroD, DCX, NKCC1, and KCC2 positive small newborn neurons in the hilus in the group with HS were less than those without HS. In the group without HS, NeuroD and NKCC1 positive newborn neurons in the SGCL were reduced in number.

Conclusions: The large newborn neurons in the hilus are immature, and the maturation of those cells continues with their migration to SGCL and reduction of cell size. In the group with HS, few mature newborn neurons were located in the SGCL and the neuronal maturation was restricted.

IMAGE: images/903442_A.jpg

IMAGE: images/903442_B.jpg

3.366

NEUROPATHOLOGY OF EPILEPSY

Ma F. Tristán Agundis[1], C. Castañeda-Gonzáles[1], J. Villeda Hernandez[2], D. Rembao Bojórquez[2], S. Palacios Escalona[3], M. C. Manzanarez Colin[3] and L. Rocha[4] ([1]Hospital Psiquiatrico "Fray Bernardino Álvarez", Mexico, Mexico; [2]Enfermedades Neurodegenerativas, Instituto Nacional de Neurología y Neurocirugía "MVS", Ciudad de México, Mexico; [3]Universidad Nacional Auntónoma de México, Ciudad de México, Mexico and [4]CINVESTAV, Ciudad de México, Mexico)

Rationale: Epilepsy is a group of disorders in the form of recurrent paroxysms of cerebral origin causing stereotypical symptoms. This disease has an autosomal dominant inheritance pattern with 60% penetrance, variable severity. Its development is multifactorial, the most common causes are disorders of development as a failure of neuronal migration, hippocampal malformations, hippocampal sclerosis and tumors.

Temporal lobe epilepsy (TLE) refers to nosological processes associated with complex partial seizures such automatism, psychological symptoms and disconnections of the medium. The incidence is 25-50 new cases per 100 000 inhabitants per year. The prevalence in America is from 500 to 1000 patients per 100 000 inhabitants. Hippocampal sclerosis is the most studied epileptogenic focus, and represents 70% of patients with TLE.

Epilepsy affects over 50 million people worldwide.

Treatment is based on drugs according to type of epilepsy surgery in specific cases.

Methods: We studied eight autopsy cases with diagnosis of temporal lobe epilepsy. We reviewed medical records and postmortem tissues, tissues were stained with hematoxylin-eosin, silver impregnation and immunohistochemistry for GFAP and examined photomicroscope.

The cases studied were of both sexes with an age range of 20 to 76 years. The weight of the brains vary between 780 and 1250 grams.

Results: All cases have developmental defects and failure of neuronal migration, neuronal depoblación, branched axons, neuronal dysplasia, heterotopias in cortex and white matter, cerebellar hypoplasia and dysplastic Purkinje neurons. There are also changes as neuronal death, hamartomatous vessels, demyelination, and degeneration depoblación Purkinje neurons.

The cases have poor circulation changes related to hypoxia, and reactive astrocytes, gliosis, pyknosis, dendrites and bodies altered starch.

Those with tuberous sclerosis show microcephaly, irregular gyri, neurofibrillary plaques, globose cells, and neuritic plaques.

Tuberculosis cases observed neurons with karyorrhexis, globose cells, axons undulate, branched axons and parenchymal and meningeal tuberculosis.

The case presents oligophrenia frontal lobe sclerosis, white matter atrophy with cyst formation, persistence of cavum septum, reduction of the cerebellar tonsils, signs dehipoxia, depoblacion neuronal and cortical spongiosis.

Conclusions: Epilepsy is a disease of multifactorial origin that begins with a neurodevelopmental defect, so the importance of research in developmental biology for this disease, as well as advice to relatives and genetic counseling.

Monday, December 6, 2010

Investigators' Workshop Afternoon Session
3:15 p.m.-4:45 p.m.

IW.15

ENDOGENOUS REGULATION OF GROUP I MGLUR-MEDIATED EPILEPTOGENESIS

Lisa R. Merlin[1], Randi J. Hagerman[2], Eric Klann[3] and Henri Tiedge[1] ([1]The Robert F. Furchgott Center for Neural and Behavioral Science, Departments of Neurology, Physiology, and Pharmacology, SUNY Downstate Medical Center, Brooklyn, NY; [2]M.I.N.D. Institute, University of California at Davis, Sacramento, CA and [3]Center for Neural Science, New York University, New York, NY)

Summary: Activation of group I metabotropic glutamate receptors (mGluRs) can have deleterious long-lasting effects on hippocampal network excitability, enhancing its propensity for producing seizure-length synchronized discharges. Under normal circumstances, however, there appear to be built-in regulators that help prevent this epileptogenic process from proceeding. In this Investigator's Workshop, Randi Hagerman will kick off the session, setting the stage for the clinical relevance of group I mGluR-mediated epileptogenesis by describing the pathophysiology and resultant phenotype of Fragile X syndrome (FXS), a condition that results from group I mGluR hyperexcitability. With Eric Klann's presentation, we will return to basic science to understand the signaling pathways that couple group I mGluRs to translation initiation, and we will explore the relevance of such pathways to FXS. Finally, Henri Tiedge will conclude by discussing endogenous regulators of group I mGluR signaling (BC RNAs and the Fragile X mental retardation protein) and the phenotypical consequences of their functional interactions. Lisa Merlin, who was among the first to demonstrate the epileptogenic properties of the group I mGluRs, will serve as moderator for this session.

Monday, December 6, 2010

Pediatric Epilepsy Highlights Session
4:00 p.m.-5:30 p.m.

1.019

THE ANTIEPILEPTIC EFFECT OF A KETOGENIC DIET IS MEDIATED BY ADENOSINE A1 RECEPTORS

Susan Masino[1], T. Li[2], A. Rahman[2], B. B. Fredholm[3], J. D. Geiger[4] and D. Boison[2] ([1]Neuroscience/Psychology, Trinity College, Hartford, CT; [2]Neurobiology, Legacy Research, Portland, OR; [3]Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden and [4]Pharmacology, Physiology and Therapeutics, University of North Dakota School of Medicine and Health Sciences, Grand Forks, ND)

Rationale: The ketogenic diet is a high-fat, low-carbohydrate regimen that reduces seizures through as yet ill-defined mechanisms. This metabolic therapy can be effective in medically refractory epilepsy, suggesting that a ketogenic diet achieves its anticonvulsant effects via mechanisms other than those targeted by traditional antiepileptic drugs.

Adenosine is an endogenous anticonvulsant and a key link between metabolism and neuronal activity. Similar to a ketogenic diet, adenosine can stop pharmacoresistant seizures. We hypothesized that adenosine acting via inhibitory adenosine A1 receptors (A1Rs) plays a key role in the anticonvulsant effects of a ketogenic diet.

Methods: To test this hypothesis, we used three types of transgenic mice, all with spontaneous electrographic seizures that are due to decreased A1R signaling: (1) mice with a complete absence of A1Rs (A1R-/-); (2) mice with a significant reduction in A1Rs (A1R+/-, a heterozygote with 50% of normal A1R levels); and (3) mice with a transgenic overexpression of adenosine kinase (Adk-tg), an intracellular enzyme that serves as a major negative regulator of extracellular levels of adenosine. Intrahippocampal electrodes recorded seizure frequency and duration after 3 weeks of maintenance on either a control or a ketogenic diet. To determine the extent to which changes in the frequency and duration of spontaneous seizures were due specifically to the low carbohydrate nature of the KD, we administered intraperitoneal injections of a 30% glucose solution.

Results: In transgenic mice with spontaneous recurrent seizures due to an adenosine deficiency but with intact A1Rs (Adk-tg), a ketogenic diet nearly abolished spontaneous seizures and reduced their duration significantly. In contrast, spontaneous recurrent seizures triggered by reduction or deletion of A1Rs were partly or completely resistant to ketogenic diet therapy, respectively. In mice which displayed reduced seizures after KD treatment we found that an injection of glucose restored seizure frequency to normal levels within 30 to 90 minutes.

Conclusions: These data suggest that a ketogenic diet reduces seizures by increasing A1R-mediated inhibition, and that this effect depends on the low carbohydrate nature of the diet. Revealing an A1R-dependent component provides new insight into the anticonvulsant mechanisms underlying the anticonvulsant effects of a ketogenic diet. Furthermore, these results suggest that ketogenic metabolism increases the activity of adenosine at the A1 receptor subtype, and could offer insight into therapies for other clinical conditions where adenosine is known to have clinical benefits.

1.179

LOCALIZATION OF PEDIATRIC SEIZURE SEMIOLOGY: A REVIEW OF 1008 SEIZURES

Martina Vendrame[1], M. Zarowski[1,2], A. V. Alexopoulos[3], S. V. Kothare[1] and T. Loddenkemper[1] ([1]Epilepsy and Clinical Neurophysiology, Children's Hospital Boston, Boston, MA; [2]Polysomnography and Sleep Research Unit, Poznan University of Medical Sciences, Poznan, Poland and [3]Neurology, Cleveland Clinic, Cleveland, OH)

Rationale: There is extensive historical and current practical evidence supporting the notion that different seizure semiologies relate to specific anatomical localizations. However, to our knowledge, no systematic analysis of the corresponding electrographic (EEG) data in seizures of different semiology has been reported. The aim of this study was to evaluate the relationship between semiology of seizures in children and adolescenet to the corresponding localization.

Methods: Charts of 225 consecutive pediatric epilepsy patients undergoing Video-EEG monitoring (VEM) over 2 years were reviewed. Seizure semiology recorded during VEM was classified according to ILAE seizure semiology terminology and EEG localization, and analyzed based on onset as defined by the EEG data (generalized, frontal, temporal, parietal, occipital or a combination of different lobes). Statistical analysis (binominal test) was performed using SPSS (version 16.0).

Results: A total of 1008 seizures were analyzed in 225 children, mean age was 8.5 years ± 5.7 (range 0-20), with 50% girls. Auras and seizures with automatisms arose predominantly from the temporal lobes ($p<0.001$). Tonic, clonic and tonic-clonic seizures had most commonly generalized onset ($p<0.001$). Hypomotor seizures were most frequently seen from the frontal lobes ($p<0.001$). Hypermotor seizures had most commonly multiple lobes or temporal onset ($p<0.001$ and $p<0.05$ respectively). Atonic, myoclonic seizures and spasms had almost exclusively generalized onset ($p<0.001$). Gelastic seizures had only generalized onset ($p<0.001$). Dyscognitive seizures had most commonly generalized or temporal onset ($p<0.001$). Versive seizures had a strong association with multiple lobes being involved at onset ($p<0.001$).

Conclusions: Different seizure semiologies relate to specific brain regions, as identified electrographically. Findings based on EEG provide important information on the seizure epileptogenic zone and seizure propagation, although seizure freedom after resection remains the 'gold standard' for localization. Semiology of seizures can provide important information for epilepsy localization, and should not be overlooked especially in patients undergoing pre-surgical evaluation.

1.255

ADJUNCTIVE THERAPY WITH LACOSAMIDE FOR EXTREMELY REFRACTORY EPILEPSY IN CHILDREN

Mary Gustafson[1,2] and F. J. Ritter[2,3] ([1]Children's Hospitals and Clinics of Minnesota - St. Paul, St. Paul, MN; [2]Minnesota Epilepsy Group, PA, St. Paul, MN and [3]Neurology, University of Minnesota, Minneapolis, MN)

Rationale: Lacosamide (LCM) is approved as adjunctive therapy in adults 17 years and older for partial onset seizures. LCM may benefit children who have failed to respond to previous antiepileptic drugs (AEDs). However, little is known about the use of LCM in children. We have reviewed our records and report our experience on dose, efficacy and adverse effects of LCM in children.

Methods: Following IRB approval, patients < 17 years old who had been treated with LCM between May 2009 and May 2010 were identified. Medical records were audited for demographics, EEG/MRI, seizure type/frequency, previous/current treatments for seizures, and information regarding treatment with LCM, dosing regimen, efficacy and adverse effects (AEs).

Results: Thirty patients (15 female, 15 male), median age 8 years (range: 17 months-16 years), were treated with LCM. 22/30 (73%) have a significant related structural abnormality identified on MRI and 21 (70%) have severe/profound cognitive impairment. Median failed past AED trials 10(range 5-18). LCM was added to 1-5 concomitant AEDs (90% e" 2 AEDs). The mean starting dose was 2.2 (range: 0.54-8.64) and maximum dose 8.4 (range: 2.74-18.8) mg/kg/day. 7/30 (23%) had a e" 50% reduction of seizures from baseline (mean dose 7.8 mg/kg/day) with 2 (6.6%) seizure free for 52 and 37 weeks. 18/30 (60%) continue LCM with duration of therapy at last contact of 4-52 weeks. 16/30 (53.3%) reported 26 total AEs regardless of association to LCM (mean dose 8 mg/kg/day) compared to 14/30 without AEs (9 mg/kg/day). Most frequently reported: ataxia (23.3%), sedation (23.3%), vomiting (10%) at mean doses of 10, 9 and 15 mg/kg/day respectively. 16/30 (53%) had LCM added to a regimen containing an AED with a primary mechanism of voltage-gated Na+ channel blocker. 10/16 (62.5%) reported AEs (7/

10 LTG, 1/3 OXC, 1/2 CBZ, 1/1 RUF): mean dose 5.24 mg/kg/day (LTG group) and 13.73 mg/kg/day (others combined). 14/30 patients whose LCM was added to non-primary Na+ channel blocker AEDs, 6 reported AEs (mean dose 8.2 mg/kg/day). No significant abnormal lab values or serious AEs were reported. EKG was not routinely performed. 12/30 (40%) discontinued LCM. 9/30 (30%) due to lack of acceptable benefit and 3 (10%) due to AEs (mean maximum dose 8.9 and 3.3 mg/kg/day respectively). 7/30 had 9 random LCM levels drawn. Levels of 1.8-8.3 mg/L were documented on 3.67 - 14.2 mg/kg/day and not clearly associated with efficacy or tolerability.

Conclusions: Lacosamide demonstrated efficacy and tolerability as adjunctive therapy in children with refractory epilepsy. Almost one in every 4 patients had a e" 50% improvement in seizure control with 2 patients (6.6%) seizure free. There were no serious adverse effects; no clinically significant abnormal lab values. In this very small group, more AEs were observed at relatively lower doses when LCM was added to LTG. When LCM is added as adjunctive therapy to multi-AED therapy, in general, an initial starting dose of 2 mg/kg/day to a maintenance dose of up to 8 mg/kg/day is tolerated.

2.001

HIGH RESOLUTION COPY NUMBER VARIATION OF ION CHANNEL GENES IN EPILEPSY

Alicia M. Goldman[1], T. L. Klassen[1], W. Gu[2], F. Zhang[2], V. Bomben[1], T. T. Chen[1], J. R. Lupski[2] and J. L. Noebels[1,2] ([1]Neurology, Baylor College of Medicine, Houston, TX and [2]Molecular and Human Genetics, Baylor College of Medicine, Houston, TX)

Rationale: Single nucleotide genetic variation is a known source of familial and sporadic disease. Recent evidence shows that the frequency of de novo genomic rearrangements, including copy number variations (CNVs) is about four orders of magnitude greater than the rate of nucleotide-based mutations. The important contribution of CNVs to epilepsy phenotypes is only now being recognized with the application of array based whole genome comparative hybridization (aCGH) platforms. Ion channel genes, despite their relative abundance and critical function in the excitable network, have been underrepresented in whole genome scans. Given the high incidence of Mendelian channel variants in epilepsy, we designed a custom CNV chip targeting this candidate gene superfamily, which represents ~1% of the genome.

Methods: We developed a custom built ion channel gene-specific comparative hybridization array (ICCH array) that interrogates all known exons in 247 human ion channel subunit genes, and used the chip to screen a cohort of 47 patients with idiopathic epilepsy.

Results: We identified 183 duplications affecting 56 channel genes with an average of four duplications per individual, and 169 deletions affecting 30 genes with an average of 3.6 deletions per individual. We observed that chromosomes and genes differed in their likelihood of being affected by CNVs. CNV variation was observed in known human epilepsy genes as well as in ion channel genes previously unlinked to human excitability disorders, thus identifying novel candidate disease genes.

Conclusions: Our targeted gene array project is the first to survey all known ion channel genes at high resolution for structural aberrations with unprecedented sensitivity. With the new platform we can move beyond single nucleotide polymorphisms to study a new dimension of genetic variation contributing to epilepsy. The ICCH array represents an innovative, rapid, and cost effective approach for uncovering novel disease mechanisms from a defined gene set and discovering novel ion channel disease genes.

Supported by NIH (AG, JLN) and Mcknight Brain Disorders Award (JLN).

2.031

PERIODIC LATERALIZED EPILEPTIFORM DISCHARGES (PLEDS): CLINICAL SIGNIFICANCE, NEUROIMAGING FINDINGS, ETIOLOGY, AND OUTCOME IN 51 INFANTS AND CHILDREN

Ajay Gupta and A. N. Moosa (Pediatric Epilepsy/Neurological Institute, Cleveland Clinic Foundation, Cleveland, OH)

Rationale: In adult series periodic lateralized epileptiform discharges (PLED) have usually been reported transiently during acute stroke, infection, or hypoxic encephalopathy. Data on PLEDs in children are limited to small case series. We report clinical and radiological features of 51 children (<18 years) with PLEDs on a scalp EEG.

Methods: The EEG database at the Cleveland Clinic from 1990-2000 was searched using the key word "PLED". Patients < 18 years were identified and their medical records and brain imaging were reviewed.

Results: 89 EEGs on 51 children (6 days to 18 years, median 6.5 years) showed unilateral or bilateral PLEDs. In 14 of 51 (27%), PLEDs occurred after an acute or subacute neurological illness in previously healthy children (acute group) with acute infections and stroke being the most common etiologies. In the remaining 37 children (73%), PLEDs were seen in the setting of a pre-existing neurological illness (chronic group). All children in the chronic group had developmental delay and neurological deficits. In the chronic group, 14 (37%) developed new PLEDs (acute on chronic group) during seizure recurrence with or without status epilepticus while 23 (62%) had no acute worsening in their neurological status and PLEDs were a chronic finding in the setting of a malformation of cortical development (9), prior epilepsy surgery (7, no PLEDs before surgery), encephalomalacia from remote trauma (2) or stroke (2), and metabolic encephalopathy (2). Children with remote epilepsy surgery (n=7) were seizure free despite post-operative PLEDs. All other children in the chronic group had epilepsy. Mortality was high with 9 deaths out of 28 (32%) in acute and acute on chronic group compared to 2 out of 23 (8.5%) with chronically present PLEDs. Of 23 with chronically present PLEDs, 22 children had an EEG and clinical follow-up for 5 months to 9 years (median 4.5 years). 2 with metabolic disease died (both had BiPLEDs), 4 underwent hemispherectomy (3) or fronto-parietal resection (1) with disappearance of PLEDs and seizures after surgery, 7 with remote epilepsy surgery were seizure free, and 9 with inoperable MCD, remote head trauma and infarcts continued to have PLEDs or BiPLEDs and chronic persistent seizures on follow-up EEGs.

Conclusions: While acute brain injury remains an important cause, PLEDs in children are more likely to be associated with preexisting chronic neurological condition with or without acute exacerbation. This recognition is important to avoid over emphasis on EEG, and relying on the clinical evaluation to guide further management in children.

2.097

INTELLIGENCE RELATES TO STRUCTURAL INTEGRITY OF NORMAL APPEARING WHITE MATTER IN TUBEROUS SCLEROSIS COMPLEX

Suzanne M. Koudijs[1], J. S. van Campen[1], O. B. Braams[2], A. Leemans[3], O. van Nieuwenhuizen[1], K. P. Braun[1] and F. E. Jansen[1] ([1]Department of Child Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Center, Utrecht, Netherlands; [2]Department of Child Neuropsychology, Rudolf Magnus Institute of Neuroscience, University Medical Center, Utrecht, Netherlands and [3]Image Science Institute, University Medical Center, Utrecht, Netherlands)

Rationale: To study the relation between intelligence and diffusion tensor imaging (DTI) characteristics of normal appearing white matter (NAWM) in children with tuberous sclerosis complex (TSC).

Methods: In 26 children with clinically definite TSC intelligence quotients (IQ) or developmental quotients were related to DTI characteristics of NAWM. Whole brain tractography was performed, and fractional anisotropy (FA), apparent diffusion coefficient (ADC), radial diffusivity (RD) and axial diffusivity (AD) were calculated for well-defined segments of white matter tracts. Neuropsychological examination was performed, closely in time to the MRI, to assess intelligence or developmental quotients.

Results: Corrected for age, a significant inverse correlation ($p<0.01$) was found between IQ and ADC in mesiotemporal, frontal and occipital NAWM tracts. In addition, IQ correlated positively with FA in corpus callosum and fronto-occipital tracts. In all supratentorial commissural and association tracts RD was inversely correlated with IQ ($p<0.01$).

In summary, DTI characteristics of infratentorial tracts and ascending or descending projection fibers showed no correlation with intelligence, as compared with supratentorial association and commissural fibers.

Conclusions: DTI characteristics of supratentorial NAWM tracts are related to intelligence in children with TSC. These findings suggest that cognitive dysfunction is, at least partly, related to a disturbed integrity of the NAWM in TSC, reflecting widespread microstructural abnormalities of white matter that are not visible on conventional MRI. Thus, white matter architecture, and not tuberload alone, is an important determinant for intelligence, adding to our understanding of the underlying pathogenesis in TSC.

2.221

EFFECT OF EVEROLIMUS ON SEIZURE ACTIVITY IN PATIENTS WITH TUBEROUS SCLEROSIS (TS)

Darcy Krueger[1], M. M. Care[1], K. Holland-Bouley[1], K. Agricola[1], C. Tudor[1], P. Mangeshkar[1], A. Weber-Byars[1], T. Sahmoud[2] and D. N. Franz[1] ([1]Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH and [2]Novartis Pharmaceuticals, Florham Park, NJ)

Rationale: TS is characterized by hamartoma formation in multiple organ systems and disabling neurological disorders including epilepsy, mental retardation, and autism. Neurosurgical resection with its associated complications and comorbidities is the current standard treatment for intractable epilepsy associated with TS. Recently, an open-label, phase II trial (NCT00411619) of everolimus, an orally bioavailable selective mTOR inhibitor, demonstrated a significant reduction in both subependymal giant-cell astrocytoma (SEGA) and tuber volume and was well tolerated. Secondary endpoints included potential changes in seizure frequency in patients treated with everolimus.

Methods: Patients e"3 years of age with a definitive TS diagnosis and evidence of serial SEGA growth (on MRI) were treated with everolimus 3 mg/m^2/d orally (titrated to tolerability to achieve target trough concentrations of 5-15 ng/mL). The primary efficacy endpoint was change in SEGA volume from baseline to 6 months.

Results: Twenty-eight patients were enrolled; median duration of treatment was 21.5 months (range 4.7-34.4). After 6 months of treatment, 21 patients (75%) had e"30% reduction in primary SEGA volume. Based on caregiver observation, the proportion of patients with daily seizures was reduced from 7 of 26 patients (26.9%) at baseline to 2 of 25 patients (8.0%) at month 6 and 1 of 25 patients (4.0%) at month 12. Of 16 patients with uncontrolled epilepsy for whom video-electroencephalogram data were available, captured electroclinical and electrographic seizures were diminished at month 6 compared with baseline (average 2.75 vs. 6.30 per 24-hour period, respectively; $p = 0.022$); 9 patients had decreases in seizure frequency (across all types of seizure), 6 had no change (all were event-free at both time points), and 1 had an increase. Interictal epileptiform activity during the first 15 minutes of stage II sleep also was reduced compared with baseline (median change -20.0 [range, -227 to 201]). Of the 9 patients who experienced a reduction in seizure frequency, evaluation of antiepileptic drug concentrations in the blood demonstrated minimal variations between pre- and posttreatment despite adjustments in dosage. Changes in seizure frequency would therefore appear to be attributable to everolimus therapy.

Conclusions: Everolimus significantly reduced seizure frequency in patients with TS. Based on these findings, everolimus may be a viable alternative to surgical resection for the treatment of intractable epilepsy in patients with TS, and additional research is warranted.

2.270

TEMPORAL LOBE EPILEPSY SURGERY IN CHILDREN: CONSIDERATIONS FOR PROGNOSTIC PREDICTORS

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Rationale: Many reports demonstrate the possibility of favorable outcome following temporal lobe epilepsy surgery. Data varies by center, but seizure freedom or significant reduction in seizure frequency is reported previously. We aim to review the outcome data in our institution for temporal lobe epilepsy surgery in younger age (less than 20 years of age) in order to determine indicators for favorable outcome.

Methods: We retrospectively reviewed the epilepsy surgery data base who underwent temporal lobe resection due to intractable epilepsy between 1992 and 2009 at the Medical College of Georgia. We examined demographic data, clinical history, EEG, MRI, neuropathology, and follow up at 1, 3 and 5 years with Engle classification. We focused the analysis on resection types and tissue diagnosis by postsurgical neuropathological examination. Surgical types were categorized as anterior temporal lobectomy (TL), lesionectomy (Le), amygdalohippocampectomy (AH), and temporal lobectomy with sparing of the hippocampus (TLwo). Pathology was categorized as mesial temporal sclerosis (MTS), cortical dysplasia (CD), gliosis (G),

tumor (T) and dual pathology (D). Statistical analysis was done by ANCOVA.

Results: Ninety cases (mean age, 12.9 years; range 0.5 and 20 years of age) were included; 51 males, 39 females. Of the 90 cases (Lt 52, Rt 38), there were 64 TL, 14 TLwo, 8 Le, and 4 AH. Combining all surgical types, good outcome (Engel I or II) was achieved in 94.4% (85/90) at one year, 87.8% (72/82) at year three, and 81.7% (49/60) at year five follow up. Separate analysis of the surgical types reveals better outcome in the TL group with good outcome in 98% (63/64) at one year, 91.5% (54/59) at 3 year, and 83.3% (40/48) at five year. In contrast, poorer outcome was observed in the TLwo group (Lt 11, Rt 3) with good outcome being achieved in 78.6% (11/14) at one year, falling to 69% (9/13) at three year, and to 67% (4/6) at five year follow up (p=0.09). Thirty one (34%, Lt 22, Rt 9) of the patients required invasive monitoring with depth electrode and grid placement prior to resective surgery. Reviewing pathology, 28 patients had MTS, 16 with cortical dysplasia, 9 with tumors, 14 with gliosis, and 23 with dual pathology. Those with MTS had the best outcome with persistent benefit, 100% (28/28) good outcome at 1 year, 96% (26/27) at 3 year, and 95% (20/21) at 5 year. The presence of gliosis indicated a propensity to lose seizure control over time, with 1 year good outcome in 92% (13/14). However, at 3, 5 years, the benefit dropped to 70% (7/10) and 62.5% (5/8) respectively. A similar trend was noted in dual pathology as well as cortical dysplasia (p=0.14).

Conclusions: We conclude that TL with the presence of MTS has the favorable outcome with sustained benefit. The poor outcome was observed in patients with TLwo. The presence of MTS has tendency of the better outcome while gliosis offers a poorer predictive outcome.

2.304

CENTRO-MEDIAN DEEP BRAIN STIMULATION (CM-DBS) IN PATIENTS WITH REFRACTORY SECONDARY GENERALIZED EPILEPSY PREVIOUSLY SUBMITTED TO CALLOSAL SECTION

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Rationale: Vagus nerve stimulation and callosal section are the available palliative surgical options in patients with secondary generalized epilepsy. DBS has been increasingly used in the treatment of refractory epilepsy over the last decade. We report on the outcome after CM-DBS in patients with generalized epilepsy who had been previously treated with extended callosal section.

Methods: Six consecutive patients with generalized epilepsy who were previously submitted to callosal section and had at least 1 year of follow-up after deep brain implantation were studied. Age ranged from 10 to 44 years. All patients were submitted to bilateral CM thalamic DBS. Post-operative CT scans documented the electrode position in all patients. All patients had pre- and post-stimulation prolonged interictal scalp EEG recordings, including spike counts. Attention level was evaluated by means of the SNAP-IV questionnaire. The pre-implantation anti-epileptic drug regimen was maintained post-operatively in all patients. Continuous stimulation was carried out using 300usec, 130Hz, 4-6V pulses.

Results: Post-operative CT documented that all electrodes were correctly located. There was no morbidity or mortality. Seizure frequency reduction ranging from 55 to 95% and increased attention level was seen in all patients. Interictal spiking frequency was reduced from 25 to 95%, but their morphology remained the same. There was re-synchronization of interictal discharges during slow-wave sleep in 3 patients.

Conclusions: All patients benefit from the procedure. The CM seems to play a role in modulating the epileptic discharges and attention in these patients. On the other hand, it is not the generator of the epileptic abnormality and appeared not to be involved in non-REM sleep-related interictal spiking modulation.

2.338

PREVALENCE OF SLEEP DISORDERS SYMPTOMS IN CHILDREN WITH EPILEPSY AND TYPE 1 DIABETES

Joshua Baron[1,2], R. A. Levy[1], B. E. Ostrander[1] and C. Ray[1] ([1]Pediatrics, Rush University Medical Center, Chicago, IL and [2]Pediatrics, John H. Stroger Hospital of Cook County, Chicago, IL)

Rationale: Children with epilepsy have a higher rate of impaired sleep than normal children, including altered sleep architecture and reporting symptoms of disordered sleep. The aim of this study was to compare the prevalence of sleep disorder symptoms in children with epilepsy versus controls and another chronic condition, type 1 diabetes (DM), to ascertain specificity to epilepsy.

Methods: After obtaining IRB permission from Rush Medical Center and Stroger Hospital, the Pediatric Sleep Questionnaire was administered to parents of children 2-18 years old with epilepsy (n=71), normal children (n=52) and children with DM (n=25). Subjects were recruited from child neurology, pediatrics and endocrinology clinics. Between-group analyses were completed using chi-square tests to compare the frequency of symptoms on the questionnaire. Using the Bonferroni correction, significance was established if $p<0.001$.

Results: Patients with Epilepsy vs. Controls:

The mean age of patients with epilepsy was 9.7 years (SD=4.3) and was 7.1 years (SD=4.1) in controls. Children with epilepsy were significantly more likely to have difficulty with sleep ($p<0.001$). Symptoms of sleep-disordered breathing were more likely in children with epilepsy, including apnea (20% vs. 0%), shaking the child to get him to breathe and awakening with a snort (all $p<0.001$). Restless sleep, leg restlessness, brief kicks of the legs and repeated kicks of the legs (26% vs. 10%) were more likely in children with epilepsy (all $p<0.001$). Teeth grinding, but not other parasomnias, was seen more in the epilepsy group (50% vs. 27%; $p<0.001$). Bedtime rituals and routines were seen more frequently in children with epilepsy, as were awakening more than twice per night and trouble falling asleep after awakening (all $p<0.001$). Symptoms of daytime hypersomnolence were also more likely, including waking up unrefreshed (53% vs. 27%), feeling sleepy, an irresistible urge to nap (38% vs. 12%) and having a teacher say the child appears sleepy (45% vs. 6%) (all $p<0.001$). Parents of children with epilepsy were more likely to have trouble awakening their children (42% vs. 21%; $p<0.001$).

Patients with Epilepsy vs. Patients With DM:

The mean age of DM patients was 13.3 years (SD=4.0). All of the significant differences between patients with epilepsy and controls were maintained in comparing patients with epilepsy and DM (all $p<0.001$), with the exception of awakening unrefreshed and being hard to awaken in the morning. Additionally, patients with epilepsy were more likely than patients with DM to snore, breathe loudly and nap (all $p<0.001$).

Conclusions: This study suggests that patients with epilepsy are at an increased risk for daytime hypersomnolence and sleep disorders, including sleep-disordered breathing and periodic limb movements of sleep, compared to controls. It also suggests that these risks are not due to the burden of having a chronic condition alone. This is an important finding, as impaired sleep may decrease seizure threshold, perpetuating further seizures in children with epilepsy and prompting further workup and treatment of specific sleep disorders.

3.007

BLOCKING EARLY GABA DEPOLARIZATION WITH BUMETANIDE RESULTS IN PERMANENT ALTERATIONS IN CORTICAL CIRCUITS AND SENSORIMOTOR GATING DEFICITS

Doris D. Wang and A. R. Kriegstein (University of California, San Francisco, CA)

Rationale: The highest incidence of seizures occurs during the neonatal period when immature networks are hyperexcitable and susceptible to synchronized activity. During development, GABA, the primary inhibitory neurotransmitter in adults, excites neurons due to high expression of the Na^+-K^+-$2Cl^-$ cotransporter (NKCC1). NKCC1 facilitates seizures because it renders GABA activity excitatory through intracellular Cl^- accumulation, while blocking NKCC1 with bumetanide suppresses seizures. Bumetanide is currently being tested in clinical trials for treatment of neonatal seizures.

Methods: Pregnant mice and their postnatal pups were treated with daily intraperitoneal injections of bumetanide at 0.2 mg/kg. We performed whole-cell patch clamp recordings in cortical pyramidal neurons to record miniature postsynaptic current to assess for synaptic connectivity. We studied neuronal morphology by using in utero electroporation of GFP-expressing plasmids and 3D reconstruction of their morphology using confocal microscopy. We also performed a battery of behavioral tests to assess for any developmental and permanent functional deficits in treated mice.

Results: By blocking NKCC1 with bumetanide during cortical development, we found a critical period for the development of AMPA synapses. Disruption of GABA signaling during this window resulted in permanent decreases in excitatory synaptic transmission and sensorimotor gating deficits, a common feature in schizophrenia.

Conclusions: Our study identifies an essential role for GABA-mediated depolarization in regulating the balance between cortical excitation and inhibition during a critical period and suggests a cautionary approach for using bumetanide in treating neonatal seizures.

IMAGE: images/902257_A.jpg

Blocking NKCC1 with bumetanide during a critical period disrupts the balance of excitatory and inhibitory synapses in the adult. (A) and (B) Current traces of mPSCs of layer II cortical neurons recorded from 4 week old and adult mice treated with either saline (PBS) or bumetanide from E15-P7. Traces on the right represent expanded segments of traces on the left. (C) Frequency of AMPA (left) and GABA (middle) mPSCs for different windows of bumetanide exposure. Ratio of GABA to AMPA mSPCs (right) shows that bumetanide treatment from E15-P7 and E17-P7 resulted in significant increases due to defects in forming excitatory AMPA synapses (D) Same parameters analyzed in (C) but in 8-12 week old adult mice. Bar graphs indicate mean ± SEM, number of recorded cells is indicated in each bar graph. (*p<0.01, **p<0.001, ***p<0.0001 compared to control; t-test).

IMAGE: images/902257_B.jpg

Bumetanide treatment causes deficits in sensorimotor gating (A) Prepulse inhibition of the startle response testing for sensorimotor gating functions. Different startle amplitudes (in newtons) in response to the 120dB stimulus (stim) are graphed against the different prepulse (pp) values. (B) Prepulse inhibition is measured by the degree to which the maximal startle response is inhibited by the prepulse stimulus. Bar graphs indicate mean ± SEM (n = 29 animals per condition). (C) Post hoc analysis of mice with similar startle response amplitudes demonstrates that even in mice matched for maximal startle, bumetanide-treated animals exhibit significant decrease in their prepulse inhibitions (D) (PBS: n=21 animals, Bum: n=29 animals; *p<0.05, **p<0.001, ***p<0.0001, two-way ANOVA for A-D).

3.261

ARE AEDS ASSOCIATED WITH SUICIDAL IDEATION?

David W. Dunn[1], C. S. Johnson[1], P. S. Fastenau[2], A. W. Byars[3], T. J. deGrauw[3], S. M. Perkins[1] and J. K. Austin[4] ([1]Indiana University School of Medicine, Indianapolis, IN; [2]Case Western Reserve University School of Medicine, Cleveland, OH; [3]University of Cincinnati College of Medicine, Cincinnati, OH and [4]Indiana University School of Nursing, Indianapolis, IN)

Rationale: In 2008, the US Food and Drug Administration issued a warning that antiepileptic drugs (AEDs) result in twice the rate of suicidal ideation as placebo and required a warning in the package insert. Experts in epilepsy, epidemiology, and mood disorders have questioned the strength of the association. We assessed suicidal ideation in children with new-onset epilepsy that subsequently were started on AEDs.

Methods: We recruited 349 children ages 6-14 years with new-onset seizures and prospectively followed them at 18 and 36 months (Austin et al 2010). These children had an estimated IQ of >55 (93%>70) and no complicating pediatric health conditions. AED use was recorded at each follow up. Caregivers completed the Child Behavior Checklist (CBCL) and children > 7.5 years completed the Child Depression Inventory (CDI). For this study we looked at question 91 (Talks about killing self - never vs. sometimes/often) on the CBCL and question 9 (I do not think about killing myself vs. I think about killing myself but I would not do it/I want to kill myself) on the CDI. The association of suicidal ideation with AED use was assessed by Chi-square or Fisher's exact test.

Results: Data from CBCL was available on 337 children at baseline, 297 at 18 months, and 276 at 36 months. Parents reported suicidal ideation in 7.2%, 6.4%, and 3.3% of children at baseline, 18 months, and 36 months respectively. There was no association between suicidal ideation on the CBCL and AED use at any time. CDI was available on 226 children at baseline, 264 at 18 months, and 271 at 36 months. Suicidal ideation was reported by 25.8% of children at baseline, 21.2% at 18 months, and 14.4% at 36 months. When we restrict to those children not on AEDs at baseline, there were increased thoughts of suicide among children currently taking an AED at 18 months compared to children not taking an AED(39% vs. 15%, p=0.003). However, by 36 months, though more children on AEDs reported suicidal ideation (24% vs. 13%), the association was not significant. No suicide attempts or completed suicides occurred during the 36-month period.

Conclusions: The prevalence of suicidal ideation reported by children is higher than that described by parents and is similar to the 20% prevalence reported by Caplan et al. (2005). Suicidal ideation was highest at baseline prior to substantial exposure to AEDS. However, we

did find an initial association between AEDs and suicidal ideation at 18 months that weakened at 36 months. Given the frequency of suicidal ideation and the potential association with AEDs, clinicians should monitor for suicidal ideation and psychopathology to reduce risk for the child and to promote quality of life.

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3.296

A DISTINCTIVE SEIZURE TYPE IN PATIENTS WITH CDKL5 MUTATIONS: HYPERMOTOR-TONIC-SPASMS SEQUENCE

Karl M. Klein[1], S. C. Yendle[1], A. S. Harvey[3], G. Wallace[4], T. Bienvenu[5] and I. E. Scheffer[1,2] ([1]Epilepsy Research Centre, Department of Medicine, The University of Melbourne, Austin Health, Heidelberg, VIC, Australia; [2]Department of Paediatrics, The University of Melbourne, Royal Children's Hospital, Parkville, VIC, Australia; [3]Department of Neurology, Royal Children's Hospital, Parkville, VIC, Australia; [4]Department of Neurology, Mater Children's Hospital, Brisbane, QLD, Australia and [5]Université Paris Descartes, Institut Cochin, CNRS (UMR8104), Inserm, U567, Paris, France)

Rationale: Recent recognition of the encephalopathy associated with CDKL5 (cyclin-dependent kinase-like 5) mutations has led to molecular diagnosis in affected girls. Onset is by 3 months of age with tonic seizures, evolving to an epileptic encephalopathy with spasms. Here, we report a distinctive complex seizure type which will facilitate diagnosis in patients with CDKL5 mutations.

Methods: Video-EEG monitoring and clinical details of 6 girls with abnormalities in CDKL5 (3 missense mutations, 2 truncation mutations, 1 deletion) were reviewed.

Results: Four of six patients with abnormalities of CDKL5 (2 missense mutations, 1 truncation mutation, 1 deletion) showed a characteristic unusual seizure type. Onset of the hypermotor-tonic-spasms sequence was between 3.5 and 13 months (median 7.5 months), between 1.5 and 11 months after seizures first began. This sequence continued at 4 years in 3 cases. Seizures were long (3.5-17 minutes) and started with an arousal from sleep followed by a quiet phase for 10-40 seconds in 3 patients. In all patients a hypermotor phase lasting 10-60 seconds followed and evolved to a tonic phase with bilateral upper limb abduction for 20-45 seconds. The seizure then evolved to a series of epileptic spasms with arms abducted and legs adducted in a cruciate posture, which lasted 2.5-15 minutes. Ictal EEG showed bilateral frontocentral beta activity evolving to bilateral delta activity with frontal or posterior maximum during the hypermotor phase, followed by diffuse attenuation during the tonic phase and high voltage transients at the vertex with diffuse attenuation during the spasms phase. These unusual seizures occurred during the epileptic encephalopathy. The clinical history and VEM in the second year of life did not suggest this sequence in the two remaining patients.

Conclusions: We highlight a distinctive, complex hypermotor-tonic-spasms sequence as a feature of CDKL5 epileptic encephalopathy. We have found that this unusual seizure type can be suspected from history alone leading epileptologists to consider the diagnosis. Video-EEG monitoring can confirm this characteristic and unusual seizure type.

Funding: NHMRC of Australia. KMK is supported by a research fellowship from the Deutsche Forschungsgemeinschaft (KL 2254/1-1) and a scholarship from The University of Melbourne.

3.337

ADOLESCENTS IN TRANSITION: DEVELOPMENTAL AND PSYCHOSOCIAL CONCERNS FOR YOUTH WITH INTRACTABLE EPILEPSY

Sarah Ahlm, H. Kaplan, A. Berg, M. Forcier and D. R. Nordli (Children's Memorial Hospital, Chicago, IL)

Rationale: The childhood onset of intractable epilepsy is often a lifelong condition, thus children must learn to assume responsibility for their own care as they approach adulthood. The purpose of this abstract is to study the developmental and cognitive attributes that contribute to this ability to assume responsibility for their epilepsy care as adults.

Methods: A social worker obtained a psychosocial assessment (PA) in a convenience sample of adolescents with intractable epilepsy seen in our outpatient clinic (5/20/08 -8/30/09). The PA combined HEADSSS screening and anticipatory guidance commonly used in Primary Care with self or parent reported transition-specific knowledge, attitudes, and skills. Information was provided by patients, parents, and medical records.

Results: 30 adolescents were included (16 male, 14 female; 15 Caucasian, 5 African American, 8 Hispanic, & 2 Other). The median age was 15.5y, range 11-23y; 15 < 16 years of age (younger) and 15 > 16 years of age (older). Cognition was assessed as within normal (7), mild to moderate impairment (18), and severe impairment (5). In older patients, cognition was assessed as within normal (3), mild to moderate impairment (10) and severe impairment (2). 23 had special education services in school.

Medical knowledge was based upon the 25 youths who were cognitively able to participate in their care. 17 had a developmentally appropriate understanding of their medical condition for their cognitive level. (9 of 12 younger, 8 of 13 older). 12 knew all of the names of their medications (6 of 12 younger, 6 of 13 older). 18 knew the purpose of their medications, (8 of 12 younger, 10 of 13 older). 5 (all older) had independently met with a medical provider (physician or nurse practitioner) in the last year. 10 acknowledged not adhering to their medication regimen as prescribed in the last year.

16 expressed an interest in intimate relationships, although only 3 acknowledged being sexually active (1 younger, 2 older). 6 acknowledged alcohol use (1 younger, 5 older) and 3 acknowledged drug use (3 older). In the previous 3 years, mental health disorders affected 15 out of 25. Of those 15 patients, 11 had internalizing disorders and 9 had externalizing disorders (5 had both types of disorders).

Conclusions: These data illustrate the types of preparedness issues faced by adolescents with epilepsy as they approach the time when

they will assume responsibility for their care. In summary, medical knowledge did not seem to increase with age and a larger than anticipated number of patients had interest in intimate relationships, drug/alcohol use and mental health needs. Awareness of these issues should help enable providers to screen for medical knowledge, mental health and risk taking behaviors. Ultimately we envision the development and implementation of programs to assist youth with epilepsy as they transition to adult care.

Platform Session A

4:00 p.m.-6:00 p.m.

A.01

MECHANISMS OF AXONAL SUPPRESSION BY HIGH FREQUENCY STIMULATION

D. M. Durand and A. L. Jensen (Neuroscience/Biomedical Engineeing, Case Western Reserve University, Cleveland, OH)

Rationale: High frequency stimulation (HFS) has been shown to be effective in the brain to suppress neural activity using deep brain stimulation electrodes for several neuronal disorders such as Parkinson's disease or epilepsy. Yet the effect of these applied currents on neuronal elements is not known and this study focusses on the suppression of axonal pathways by HFS.

Methods: Sinusoidal stimulation (sHFS) was applied to the alveus in the hippocampal slice in-vitro either in an intact slice or in isolated alveus. The compound action potentials and the evoked potentials were measured to determine how stimulation could block axons. Channel blockers and potassium concentration were also applied to the tissue to separate the various mechanisms.

Results: Five possible mechanisms were investigated: (1) field potential desynchronization, (2) elevated bath potassium, (3) the role of cellular mechanisms , (4) the suppressive effects of the neuromodulator adenosine, and (5) the hyperpolarization-activated (Ih) channel. The results suggest that the suppressive effects of sHFS were not generated by field potential desynchronization. In addition, stratum pyramidale and oriens were not required for the suppressive effects of sHFS on alvear axons. Bath applied potassium ACSF (15 mM K+) in the intact slice as well as the isolated alvear axon field produced significant axonal suppression. The suppressive effect on amplitude, width, and latency of evoked potentials were similar for both bath-applied potassium and sHFS. Finally, the neuromodulator adenosine had no effect on sHFS-mediated suppression of evoked potentials within alvear axons, nor did blocking the hyperpolarization-activated cation (Ih) conductance. Instead, application of Ih blocker ZD7288 (50 iM) lowered the threshold for complete suppression of the compound action potential using sHFS.

Conclusions: These results show that stimulus induced changes in extracellular potassium likely underlie the suppressive effects of direct sHFS on the alveus in-vitro. These data strongly suggest that potassium accumulation plays a crucial role in modulating the activity of axons activated by high frequency stimulation by serving as a neuroprotective mechanism to prevent excess, synchronous neural discharges from propagating throughout neural networks.

A.02

BABOONS AND HUMANS: COMPARISON OF EEG TRAITS FOR TRANSLATIONAL RESEARCH PURPOSES

Dorothee G. Kasteleijn-Nolst Trenite[1], C. A. Szabó[2] and J. T. Williams[3] ([1]Medical Genetics, University of Utrecht, Utrecht, Netherlands; [2]Neurology, University of Texas Health Science Center, San Antonio, TX and [3]Genetics, Southwest Foundation for Biomedical Research, San Antonio, TX)

Rationale: To compare spontaneous and photic induced epileptiform EEG abnormalities in scalp EEG recordings of a well documented, pedigreed colony of baboons at the Southwest Foundation for Biomedical Research (SFBR; San Antonio, Texas) with those of photosensitive epilepsy patients, for future extrapolation of pathophysiological studies.

Methods: Scalp EEG studies utilizing intermittent photic stimulation (IPS) were performed in 676 baboons. These studies lasted 60 minutes, and the baboons were lightly sedated (ketamine 5-6 mg/kg) from electrode placement and transfer between their cages and the primate chairs.

Scalp EEG studies were performed in a Dutch epilepsy patient population of 2313 patients: 100 (4.3 %; 61 F: Caucasians) were found to be repeatedly photosensitive and were studied in detail in comparison to 100 non-photosensitive (age- and sex- matched) patients from the same population.

Detailed data analysis with comparison of spontaneous and IPS evoked epileptiform discharges with special emphasis on onset and spreading of the discharges was performed. If no onset could be found due to fast spreading, the maximum amplitude was considered.

Results: The prevalence of seizures in the baboon colony is 20%, with an incidence of 1-2%. Witnessed seizures generally lasted 15-60 seconds, and were either myoclonic or generalized tonic-clonic. The EEGs demonstrated interictal epileptiform discharges (IEDs) in 332 (49%) of EEG studies. Most of the discharges were 4-6 Hz frequency, rarely 2-3 or 6-7 Hz. The IEDs were maximal over the fronto-central regions. Seizures were recorded in 221 (33%) baboons, and included eyelid or facial myoclonus, truncal myoclonus, rarely GTCS or absence seizures. Photosensitivity, defined by evidence of time-locked or increased IED rates as well as myoclonic seizures associated with IPS, was found in 157 (23%) of baboons. Photosensitivity was identified in 40% of the baboons with spontaneous IEDs. While the photic driving response is posteriorly predominant, the photoparoxysmal responses (PPRs) were expressed frontocentrally.

Sixty-five percent of photosensitive epilepsy patients had a history of myoclonic seizures or absences besides usually a GTCS. In those epilepsy patients with spontaneous IEDs (66%), 50% were photosensitive. The IEDs were more temporo-parieto-occipitally (170/ 259 foci, 66%) than fronto-centrally. The PPRs had an occipital onset or maximum in 64%, a temporo-parietal in 29% and were frontocentrally in only 7%.

Conclusions: While earlier electrophysiological data in the baboon Papio papio of Senegal presented by Naquet and again our scalp EEG data suggest a frontal predominance of spontaneous and IPS-induced IEDs or seizures compared to the temporo-parieto-occipital predominance in humans, further functional neuro-imaging and EEG studies might elucidate a common role of the parietal lobes in the

epileptic networks with differences in spreading pattern between the species.

A.03

SILK-BASED ADENOSINE DELIVERY: THERAPEUTIC TOOL TO PREVENT SEIZURES AND DISEASE PROGRESSION

Tianfu Li[1], E. M. Pritchard[2], D. L. Kaplan[2] and D. Boison[1] ([1]RS Dow Neurobiology Labs, Portland, OR and [2]Tufts University, Medford, MA)

Rationale: Pharmacotherapy for epilepsy is limited by drug resistance and failure to prevent development and progression of epilepsy. Adenosine is an anticonvulsant with proven efficacy in pharmacoresistant epilepsy. Consequently, adenosine augmentation constitutes a rational approach for seizure control. Due to cardiovascular side effects of systemic adenosine augmentation, focal application becomes a necessity. Using two independent rat models, hippocampal kindling and systemic kainic acid (KA), we report on the therapeutic potential of novel silk-based polymers engineered to release adenosine.

Methods: Silk-based polymers were engineered to release 250 or 1000 ng adenosine per day during a limited time span of 10 days. In the first study, rats were kindled by unilateral hippocampal electrical stimulation. Polymers releasing 1000 ng adenosine per day, or control polymers, were implanted into the ipsilateral infrahippocampal fissure either prior to onset of kindling or into fully kindled (stage 5) rats. In the second study, convulsive status epilepticus (SE) in young male rats was triggered by systemic administration of KA (12 mg/kg i.p.). At 9 weeks after SE all animals had experienced at least 10 spontaneous stage 4 or 5 seizures and the average seizure rate was 4.2±1.2 seizures per week. At this time polymers releasing 250 ng adenosine/day or control polymers were implanted into the lateral brain ventricles and animals were subjected to 4 weeks of continuous video-EEG.

Results: In fully kindled rats, recipients of adenosine-releasing implants (N=5) were protected from generalized seizures (avg. seizure stage 0.2±0.5) over a period of 10 days corresponding to the duration of sustained adenosine release. To monitor seizure-development in the presence of adenosine, adenosine-releasing or control polymers were implanted prior to kindling. After 30 stimulations (4-8 days after implantation) control animals developed convulsive stage 5 seizures, whereas recipients of adenosine implants were protected. Kindling was resumed after 9 days to allow expiration of adenosine-release. During 30 additional stimulations, rats with adenosine-releasing implants gradually resumed kindling at seizure stages corresponding to those when kindling was initially suspended, while controls kindled at convulsive seizure stages. In the KA model, seizures in recipients of adenosine implants were almost completely suppressed (avg. number of seizures 0.6±0.5; N = 10) during the first week, while seizure frequency increased in controls. Remarkably, seizure suppression in recipients of adenosine-releasing implants was maintained far beyond polymer expiration (day 10) into week 4 indicating a disease-modifying effect of focal adenosine-delivery.

Conclusions: We demonstrate that sustained focal adenosine release from silk-based brain implants is sufficient to suppress seizures in two rat models of epilepsy. In addition, suppression of kindling epileptogenesis and prolonged seizure suppression in the rat post status model suggest a novel disease modifying effect of focal adenosine delivery.

A.04

HIPPOCAMPAL MICROSEIZURES IN EPILEPTOGENESIS

Alberto E. Musto, T. M. Quebedeaux and N. G. Bazan (Neuroscience Center of Excellence, Louisiana State University, New Orleans, LA)

Rationale: Epileptogenesis is a dynamic process involving several molecular and cellular mechanisms that support the rearrangement of neuronal networks which foster the onset of recurrent seizures. High frequency oscillations (HFOs) described in the brain of epileptic animals and patients with epileptic disorders have been postulated as a predictive marker of epileptogenesis. Since HFOs represent hypersynchornized action potentials of small neuronal networks, other abnormal electrical patterns should be studied and characterized to further understand their role in epilepsy.The goal was to simultaneously characterize spontaneous neuronal oscillatory expression patterns within different hippocampal regions during epileptogenesis.

Methods: An experimental model of temporal lobe epilepsy was induced by intraperitoneal administration of kainic acid or pilocarpine in adult mice and rats. Following recovery from status epilepticus (SE), silicone probes with a 16 parallel microelectrode array were implanted in the dorsal hippocampus parallel to the CA1-dentate gyrus axis. Local field potentials from the hippocampus were recorded after being amplified, band-pass filtered (1 Hz-3 kHz) and digitalized with 12 bit resolution at continuous 50 kHz through pre-amplified headstage and system data acquisition systems. Time-dependent changes of the oscillatory activity after SE were analyzed and compared with naïve animals. Analysis included: (1) quantifying bursts of HFOs and high voltage interictal spikes (IS), (2) frequency band analysis, and (3) characterizing depth voltage and spike units train profiles, (3) microseizure (microdischarges with repetitive and evolving patterns). Video monitoring and Racine's score were used to detect spontaneous seizures and quantify seizure severity, respectively.

Results: As expected, HFO events were found in CA1 and DG regions during sleep-wake transition cycles of animals with clinical spontaneous seizures. HFOs modified the frequency of the subsequent local field potential activity. Microseizures were observed in different hippocampal layers. Most IS had a slow positive component and were located in the stratum oriens-pyramidal layers. Meanwhile, IS within the pyramidal layer and DG had high frequencies and reverse phase components. There was a high correlation between these events and a progressive disruption of the physiological voltage-versus-depth profile

Conclusions: These observations suggest that epileptogenesis involves the disruption of physiological oscillatory patterns in the hippocampus while no severe clinical seizures are present. This disruption continues to progress, impairing network inhibition, promotes seizure severity and seizure susceptibility in temporal lobe epilepsy. HFOs may participate in propagated-seizure or kindling-like mechanisms while microseizures could reflect predictive cognitive impairment.

A.05

BLOOD-BRAIN BARRIER DISRUPTION ON T1-WEIGHTED MRI IS A BIOMARKER FOR SEIZURE SUSCEPTIBILITY AFTER EXPERIMENTAL TRAUMATIC BRAIN INJURY IN THE RAT

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Rationale: Approximately 5-30% of patients with traumatic brain injury (TBI) will develop posttraumatic epilepsy (PTE), depending on injury severity. Studies to date have shown that a variety of drugs, including antiepileptic drugs, administered after injury, do not prevent the development of PTE. Establishing non-invasive MRI end-points as biomarkers of posttraumatic epileptogenesis may be of particular benefit as we continue to search for possible agents to prevent PTE. The presence of blood-brain barrier disruption (BBBD) has been increasingly indentified as a prominent contributor to epileptogenesis in multiple models of experimental epilepsy.

Methods: A total of 12 animals underwent functional neurological and MRI evaluations after either moderate-to-severe fluid percussion or sham brain injury. At three months after injury, animals were challenged with a chemoconvulsant, kainic acid, in doses lower than those used to induce status epilepticus to assess post-injury provoked seizure susceptibility.

Results: Gadolinium-enhanced T1-weighted MRI evaluations of injury-related BBBD reliably distinguished between injured and sham-injured animals at 72 hours after injury. BBBD at 72 hours after injury was also significantly correlated with total number of seizures in the first 60 minutes after kainate administration and with latency to seizure onset ($r= 0.738$, $p= 0.010$ and $r= - 0.758$, $p= 0.007$, respectively).

Conclusions: Our MRI-based protocol (including pre- and post-gadolinium T1 scans) for assessing TBI-related BBBD is reliable and has a unique advantage over commonly used methods due to its non-invasive nature. The strong correlation between the MRI-based BBBD end-points and post-injury seizure susceptibility supports its use as a biomarker for posttraumatic epileptogenesis. The potential of this information for improving our clinical standard-of-care protocols to predict long-term risk of developing PTE may be significant. Preclinical MRI biomarkers could be used to guide future study designs by increasing the similarity of preclinical to radiographically-based, clinical patient selection protocols and may enhance translation of potential therapies directly into the clinics.

A.06

ANTIEPILEPTIC ACTIONS OF A NOVEL AMPA GLUR1 SPLICE MODULATING OLIGOMER IN A MODEL OF NEONATAL SEIZURES

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Rationale: Up to 30% of epilepsy associated ion channel genes demonstrate altered splicing, including AMPA receptor GluR subunits, which exist as mutually exclusive alternatively spliced 'flip' or 'flop' variants. GluR1 flip has higher glutamate sensitivity than GluR1 flop, thus increasing GluR1 flip would lead to network hyperexcitability and increased seizure susceptibility. Post-seizure increases in GluR1 flip are implicated in the pathogenesis of seizures and epilepsy, and reducing GluR1 flip levels should have potent antiepileptic and antiepileptogenic actions. This is particularly important in the neonatal period where GluR expression peaks developmentally. Splice modulating oligonucleotides (SMOs) are a class of compounds that bind to and block pre-mRNA regulatory sites to direct alternative splicing. Thus, re-direction of GluR1 pre-mRNA splicing away from flip production may provide a potent therapeutic option. We have developed a novel SMO that selectively and potently decreases GluR1 flip levels.

Methods: For all experiments and treatment groups SMO or vehicle was delivered by free hand ICV injection into both lateral ventricles of FVB mouse pups on postnatal (P) days P1, P3, and P5, with evaluation at P10. We determined SMO dose-response for GluR flip and flop levels by real-time PCR in hippocampus and cortex. For all electrophysiology experiments, whole-cell patch clamp recordings of CA1 pyramidal neurons were performed on P10 hippocampal slices. Additionally, single dose (3mg/kg) and incremental kainate IP dosing paradigms were used to evaluate SMO effect on seizure severity, latency, and threshold.

Results: ICV delivery of this SMO resulted in a dose-dependent down-regulation of GluR1 flip at P10 in cortex and hippocampus. SMO directed GluR1 flip reduction,decreased AMPA receptor-mediated excitatory post-synaptic currents (EPSCs) generated at Schaeffer collateral/CA1 synapses by about 40%, while NMDA-mediated EPSCs were unaffected. Increases in AMPA-EPSC amplitude and duration by cyclothiazide (a GluR flip specific modulator) were robustly depressed after SMO mediated knockdown of GluR1 flip, indicating GluR1 flip contributes most of the cyclothiazide-sensitive EPSC in neonatal mice. Decreasing GluR1 flip levels with our SMO provided strong protection against kainate-induced seizures in neonatal mice. Specifically, we demonstrate decreased seizure severity with SMO treatment after single kainate dose. Further, with incremental kainate dosing, SMO-treated mice required 76% more kainate to induce status epilepticus. Importantly, CA1 long term potentiation, a cellular model of hippocampal-dependent learning, was unaffected by decreasing the GluR1 flip levels.

Conclusions: We developed a highly potent and specific modulator of GluR1 alternative splicing which provided robust neonatal antiseizure activity without affecting synaptic plasticity, suggesting it may not have anti-cognitive properties. Our results show that modulation of AMPA channel alternative splicing is a novel therapeutic strategy for preventing seizures and epileptogenesis.

A.07

EEG PHENOTYPES IN AN EXTENDED BABOON PEDIGREE

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Rationale: The largest captive baboon colony in the world is housed at the Southwest Foundation for Biomedical Research (SFBR) in San Antonio, Texas. As natural epilepsy (spontaneous seizures) is highly prevalent in this colony, we used EEG to phenotype a large, accurately-pedigreed group of baboons within the colony. Some of the baboons also underwent repeat studies at least one year after their initial evaluation to assess the long-term stability of the electroclinical phenotypes.

Methods: Scalp EEG studies were performed in 676 baboons (Papio hamadryas anubis, cynocephalus and their hybrids) using minimal intramuscular ketamine (5-6 mg/kg) to sedate the animals for transfers

in and out of a primate chair and electrode placement. Intermittent light stimulation (ILS) was performed on two occasions during the one-hour study, at least fifteen minutes apart at frequencies 3-30 Hz. Each study was between 40-60 minutes in duration. The animals were classified according to conventional electroclinical phenotypes: presence or absence of interictal epileptic discharges (IEDs), seizures and photo-paroxysmal or -convulsive responses during the EEG studies. Effects of age, gender and species on EEG phenotypes were also examined. The present study was approved by the Institutional Animal Care and Use Committees of the UTHSCSA and SFBR.

Results: The classification of the animals demonstrates that IEDs were identified in 332 (49%) baboons. Seizures were recorded in 221 (33%) animals, predominantly myoclonic (eyelid, face or body), rarely generalized tonic-clonic or absence, seizures. Photosensitivity was seen in 157 (23%) baboons. Only 42% of baboons with IEDs demonstrated photosensitivity, but photosensitivity was associated with IEDs in 89%, compared to 5% of baboons without IEDs. Repeat studies at mean interval of 3 (range 1-6) years in 30 baboons whose initial studies were performed at 4 years or older were concordant for the presence or absence of IEDs or photosensitivity in 70%, respectively.

Conclusions: Spontaneous IEDs and seizures are highly prevalent in this baboon colony. Ketamine, particularly at low doses, may have slightly reduced the IED or seizure threshold. The prevalence of photosensitivity in baboons with IEDs is similar to that associated with juvenile myoclonic epilepsy. Both IEDs and photosensitivity are stable phenotypes in adolescent and adult baboons. The photosensitivity phenotype is strongly associated with the expression of IEDs. The high prevalence of IEDs in this pedigree, and the lack of gender, age or subspecies effects on the EEG phenotypes, strongly suggest that genetic factors must play a role in explaining the observed variability.

Table 1. EEG Phenotypes and Correlation with Demographic and Clinical Findings

IMAGE: tables/908037_T1.jpg

EEG = Electroencephalography

IED = Interictal Epileptic Discharge

PS = Photosensitive

PCA = Papio hamadryas anubis

PCX = Papio hanadryas anubis/cynocephalus hybrid

yo = Years old

A.08

RAPAMYCIN ATTENUATES THE INCREASES IN SEIZURE SUSCEPTIBILITY AND NEURONAL EXCITABILITY FOLLOWING NEONATAL SEIZURES IN RAT

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Rationale: Neonatal seizures are refractory to current drugs and can result in chronic epilepsy and long-term cognitive deficits. The mammalian Target of Rapamycin (mTOR), a key regulator of protein translation has been implicated in epileptogenesis in adult models of epilepsy (J Neurosci 29:6964-6972; J Neurosci 29:8259-8269). We hypothesized that the mTOR Complex 1 (mTORC1) kinase activity is developmentally enhanced during the neonatal period, coincident with heightened synaptic plasticity and increased seizure susceptibility and that post-seizure activation of the mTORC1 pathway may be critically involved in creating epileptic networks in the immature brain. We assessed the developmental pattern of the mTORC1 activity in rat hippocampus and cortex and tested the efficacy of mTORC1 inhibitor rapamycin in attenuating long-term increases in neuronal excitability and seizure susceptibility in a rat model of neonatal seizures.

Methods: The levels of mTOR and its activity readout phospho-p70S6 (Thr389) kinase (p70S6K) from postnatal day (P)3 to adulthood were quantified by western blot. Hypoxic seizures (HS) were induced by graded global hypoxia at P10. Control and HS rats were treated with rapamycin (at 3 mg/kg i.p.) or vehicle, 24h before and 1h after exposure to hypoxia. Differences in susceptibility to kainic acid (2 mg/kg, i.p.) were evaluated at 72h post-HS. Spontaneous AMPA receptor-mediated EPSCs (sEPSCs) in CA1 pyramidal neurons were recorded in ex vivo hippocampal slices removed 48h post-HS.

Results: mTOR protein expression is significantly lower during the neonatal period (P10/11) compared to adulthood (69±6.1% of adult, $n=5$, $p<0.05$ in the hippocampus, and 54±5.2% of adult, $n=5$, $p<0.001$ in the cortex). In contrast, mTORC1 activity, assessed by p70S6K phosphorylation levels, is significantly higher at P10/11, relative to adult (43.8±12.3 fold increase, $n=5$, $p<0.05$ in the hippocampus and 70.7± 8.4 fold, $n=7$, $p<0.001$ in the cortex), suggesting that in developing brain mTORC1 pathway may be critically involved in epileptogenesis. Indeed, mTORC1 inhibitor rapamycin blocked the post-HS increased seizure susceptibility, as demonstrated by significantly longer latency to onset of first behavioral seizure after kainate administration at P13 (control+vehicle: 21.73 ± 1.61 min, $n=13$; HS+vehicle: 16.35 ± 0.51 min, $n=10$; HS+rapamycin: 23.24 ± 2.21 min, $n=11$; $p=0.021$). In addition, rapamycin treatment reversed the subacute increases in sEPSCs amplitude in the CA1 pyramidal neurons in ex vivo hippocampal slices removed 48h post-HS (control+vehicle: 100 ± 6.27%, $n=6$; HS+vehicle: 137.62±3.39% of control, $n=6$; HS+rapamycin: 107.93±4.64% of control, $n=6$; $p<0.001$).

Conclusions: The mTORC1 activity peaks during early postnatal development coincident with the critical period of synaptogenesis. Acute pharmacologic suppression of mTORC1 activity disrupts subsequent increases in seizure susceptibility and neuronal excitability following neonatal seizures. The mTORC1 pathway may be a target for development of novel antiepileptogenic therapies in the immature brain.

A.09

MULTIPLEXED, HIGH-DENSITY ACTIVE ELECTRODES USING FLEXIBLE SILICON ELECTRONICS

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Rationale: In all current brain-machine interface devices for both clinical and research applications, each electrode is independently connected to separate control systems. Examples of such devices include penetrating microelectrode arrays and cortical surface electrode arrays, and systems such as deep brain stimulators and epilepsy treatment devices. These individually wired electrodes limit both the

number and configuration of the electrodes that can be used to sample and stimulate tissues. Active circuits to reduce this wiring burden are limited by the mismatch between the rigid, planar nature of conventional, silicon electronics and the irregularly shaped tissue surfaces.

Methods: Flexible electronics that are capable of intimate, non-invasive integration with the soft, curvilinear surfaces of the brain offer important opportunities for diagnosing and treating disease and for improving brain-machine interfaces.

Results: Here, we report new dense arrays of multiplexed electrodes using flexible electronics that can enable an unprecedented level of spatial and temporal electrocorticographic (ECoG) resolution over large areas of cortex. The extreme flexibility of the devices can further enable simultaneous sampling of gyral and intrasulcal ECoG to sample regions of the brain that were previously inaccessible or difficult to reach, but are known to carry enormously important information.

We demonstrate this technology in a sensor system composed of 720 silicon nanomembrane transistors configured to record electrical activity directly from the feline brain in vivo. The device samples with simultaneous submillimeter and submillisecond resolution through 360 amplified and multiplexed channels, requiring only 39 external wire connections. The design can be scaled up to much larger sizes, without dramatically increasing the number of external connections. We use this system to map visual and stimulation evoked potentials at high resolution, on the surface of primary visual cortex.

Conclusions: This demonstration is one example of many possible uses of this technology in a new generation of minimally invasive clinical and research devices for medical and brain-computer interface applications.

IMAGE: images/908296_A.jpg

Monday, December 6, 2010

Platform Session B

4:00 p.m.-6:00 p.m.

B.01

PILOT STUDY OF PARAHIPPOCAMPECTOMY: A NEW SURGICAL APPROACH, AS EFECTIVE AS SELECTIVE TEMPORAL LOBE RESECTIONS, IN MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Mesial temporal lobe epilepsy (MTLE) is the most frequent type of epilepsy encountered in epilepsy surgery centers, and surgery has the greatest proven impact on the patient's quality of life. Given parahippocampal multidirectional connectivity, its role as hippocampal output gate and potential epileptogenic role, we suggest selective resection of the parahippocampus has the same surgical results in terms of seizure control as selective amygdalohippocampectomy. However, better neuropsychological outcomes might be expected since the anatomical structure involved in semantic memory is spared.

Methods: Experimental, longitudinal, prospective study comparing selective amygdalohippocampectomy through a trans-T3 resection approach to a trans-T3 resection approach plus parahippocampectomy, (subiculum as upper limit). Presurgical evaluation was conducted according to standardized protocol, including patients with MTLE and hippocampal sclerosis. Patients were randomly selected to one or the other surgical procedure after signing an informed consent. Patients were followed up for 12 months, and evaluated using the Engel outcome scale and standard neuropsychological tests.

Results: We performed 20 procedures, 10 selective amygdalohippocampectomies and 10 selective parahippocampectomies. There was no statistical difference in seizure control at 12 months follow up, in the parahipocampectomy group 9 patients are Engel 1 and one patient IVa. Neuropsychological outcomes in semantic memory were statistically significant superior in patients subjected to parahippocampectomy.

Conclusions: Parahippocampectomy allows deafferentation of the principal afferent pathways of the hippocampus ensuring desynchronization. Hiperexcitability in patients with MTLE is reduced by disconnection of the glutaminergic circuitry. Parahippocampectomy seems to provide the same outcome in terms of seizure reduction as conventional procedures, with lesser negative impact on neuropsychological parameters. It remains to be seen if seizure control is maintained in the long term.

B.02

BILATERAL POSTERIOR PERIVENTRICULAR NODULAR HETEROTOPIA: AN INFRASYLVIAN SYNDROME

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Rationale: Periventricular nodular heterotopia (PNH) are a well recognized malformation of cortical development. Bilateral symmetrical frontally-predominant PNH form the largest group of PNH and are associated with mutations of *FLNA* in 50% of cases. However, PNH are not always anteriorly predominant and may be associated with an array of abnormalities involving posterior fossa structures. We examined the spectrum of radiological features associated with posterior predominant PNH and the clinical genetics of this malformation.

Methods: We classified the MRI scans of 45 patients with bilateral posterior PNH based on a detailed analysis of imaging findings. We defined posterior PNH as restricted to the region around the posterior horns, atria or temporal horns of the lateral ventricles. The shape, location and symmetry of PNH were analysed and the presence of all associated abnormalities was documented. *FLNA* was examined by either denaturing high performance liquid chromatography or sequencing in each patient.

Results: The cohort comprised 29 females (64%) and 16 males and included 2 sister pairs, one monozygotic twin brother pair and one mother-son pair. Ages ranged from a fetus (in-utero scan) to 67 years. 23/45 (51%) patients had posterior fossa abnormalities: 16 had dysplastic cerebella with or without cyst and 5 had morphologically normal but small cerebella. 21/45 patients (47%) had posterior fossa cysts. 35/45 (78%) had corpus callosum abnormalities: 5 agenesis and 20 with thin posterior body and splenium. 19/45 patients had decreased posterior white matter volume and 23/45 had colpocephaly. 35/45 (78%) had associated posterior / Sylvian cortical malformations or abnormalities of sulcation, including 18/45 (40%) with abnormal Sylvian fissures. No patient had a mutation of *FLNA*.

Conclusions: Posterior PNH are the second largest group of PNH and are radiologically and genetically distinct from suprasylvian/frontal PNH due to *FLNA* mutations. 98% of patients have associated brain malformations largely confined to the infrasylvian region. We therefore propose that these forms of PNH be termed "infrasylvian PNH". The malformations associated with infrasylvian PNH have a characteristic spectrum of radiological features. Evidence for a genetic basis can be drawn from the monozygotic twins, sibling pairs and mother-son pair with infrasylvian PNH who show a range of abnormalities within the infrasylvian PNH spectrum. Our observations suggest that currently unidentified genetic determinants are likely to cause the infrasylvian PNH spectrum of abnormalities.

B.03

DIFFERENT ANATOMICAL CORRELATES FOR VERBAL MEMORY IMPAIRMENT IN TEMPORAL LOBE EPILEPSY

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Rationale: Memory impairment is one of the most prominent cognitive deficits in temporal lobe epilepsy (TLE). The overall goal of this study was to explore the contribution of cortical and hippocampal (subfield) damage to impairment of auditory immediate recall (AIMrecall), auditory delayed recall (ADMrecall) and auditory delayed recognition (ADMrecog) of the Wechsler Memory Scale-III in TLE with (TLE-MTS) and without hippocampal sclerosis (TLE-no). It was hypothesized that volume loss in CA1 and CA3 and dentate gyrus (CA3&DG) determine memory impairment in TLE-MTS and temporal mesial neocortical thinning in TLE-no. Furthermore, it was assumed that frontal lateral cortical thinning aggravates memory impairment in both groups.

Methods: T1 whole brain and T2-weighted high resolution hippocampal MRI and WMS-III were acquired in 22 controls, 14 TLE-MTS and 19 TLE-no. Hippocampal subfield volumes, i.e., entorhinal cortex, subiculum, CA1, CA1-2 transition zone and CA3&DG volumes were determined on the T2 image using a manual parcellation scheme. Freesurfer was used to obtain cortical thickness averages of temporal (fusiform (FUSI), parahippocampal gyrus), frontal (superior, caudal and rostral medial gyrus, pars opercularis (POP), orbitalis and triangularis) and parietal (precuneus, inferior and superior parietal region, supramarginal gyrus) cortical regions of interest (ROI). MANOVA and stepwise regression analysis were used to identify hippocampal subfields and cortical ROI significantly contributing to AIMrecall, ADMrecall and ADMrecog.

Results: All three memory scores were significantly lower in TLE-MTS and TLE- no compared to controls but not different between the two TLE groups. In TLE-MTS, AIMrecall ($p = 0.0016$) was associated with CA3&DG, ADMrecall with CA3&DG ($p = 0.002$) and POP ($p = 0.01$) and ADMrecog with CA1 ($p = 0.023$). In TLE-no CA3&DG ($p = 0.019$) and FUSI thickness ($p = 0.029$) were associated with AIMrecall, ADMrecall with FUSI ($p = 0.044$) and POP ($p = 0.041$) thickness and ADMrecog with FUSI ($p = 0.036$).

Conclusions: The study provided evidence for a different structural correlate of the verbal memory impairment in TLE-MTS and TLE-no and thus further supports the notion that TLE-no is not just a mild form of TLE-MTS but a different entity of TLE. In TLE-MTS the impairment was associated with neuron loss in the hippocampus. CA3&DG was associated with impaired recall (AIMrecall, ADMrecall) and CA1 with impaired recognition (ADMrecog) suggesting a functional specialization by different hippocampal subfields. In TLE-no memory deficits were associated with CA3&DG and FUSI, i.e., involved a more wide-spread and less well defined hippocampal-mesial-temporal cortical regions. POP thinning, indicating frontal dysfunction, influenced ADMrecall performance in both TLE groups. Despite the different structural correlate, the memory impairment was of similar severity in both groups. This indicates that it is the interruption of the network supporting a specific function and less the anatomical localization of the interruption within the network which determines the memory impairment.

B.04

SUBTLE IMAGING FINDINGS OF THE HIPPOCAMPUS IN TEMPORAL LOBE EPILEPSY

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Rationale: The most commonly observed MRI findings in temporal lobe epilepsy (TLE) are hippocampal atrophy and T2 signal hyperintensity, the presence of either of which is a sign of hippocampal sclerosis (HS). However, most TLE patients have no obvious hippocampal MRI abnormalities. The hippocampus has many fine structural features that may be seen on high-resolution MR images, but they may be difficult to appreciate and therefore are easily overlooked. Asymmetries of these fine structural details may be evidence of underlying hippocampal abnormalities and thus may suggest the site of seizure onset in TLE patients. An asymmetric loss of differentiation of the laminar hippocampal internal architecture (HIA) has been suggested as a possible sign of hippocampal sclerosis, as has an asymmetric loss of digitation of the hippocampal head (DIG) (Figure 1), but these findings have not been well described in the literature. We examine the relationship between laterality of seizure onset in TLE patients and HIA, DIG, and asymmetric loss of dentation of the ventral surface of the hippocampus (DENT) (Figure 1).

Methods: Fifty-four patients were identified who had video-EEG proven unilateral TLE and temporal lobe protocol MRI scans with high-resolution coronal T2-weighted images that were free of significant artifact. Scans were reviewed by a single reviewer blinded to side of seizure onset. Each coronal slice through the body of the hippocampus was evaluated on each side according to a benchmarked 4-point scale of clarity of HIA from 1 = "no differentiation of HIA" to 4 = "Very Clear differentiation of HIA", and an average HIA clarity score was calculated for each side. Coronal images through the hippocampal head were

evaluated on each side for the number of visible digitations from 1 to 3. On oblique sagittal images, the degree of dentation of the ventral aspect of the hippocampus was scored on a 4 point scale for each side. Asymmetry scores were calculated for each measure by subtracting left from right. Evidence of HS was also recorded. Asymmetry scores were used in single and multiple logistic regression models to predict laterality of seizure onset for patients without evidence of HS (HS-), patients with evidence of HS (HS+), and both groups combined.

Results: When the measures were considered individually, asymmetries of HIA and DIG were each significantly predictive of the side of seizure onset in the entire group and both subgroups (Table 1). An asymmetry of DENT was a significant predictor in the whole group and the HS+ subgroup, but showed only a trend (p=0.10) in the HS- subgroup. In multivariable models, HIA asymmetry was shown to be the strongest predictor. DIG significantly contributed to the model of the whole group but did not in the HS- subgroup (p=0.09), and the sample size of the HS+ subgroup did not allow a confident estimate of significance of the multivariable model. DENT did not significantly add to the multivariable model of the combined group or either subgroup.

Conclusions: Asymmetries of HIA, DIG, and DENT are subtle imaging findings that may be seen in TLE and indicate the laterality of seizure onset.

IMAGE: tables/902593_T1.jpg

* significant at á = 0.05

IMAGE: images/902593_A.jpg

The upper left image shows loss of HIA clarity on the left. The lower left image shows prominent digitation of the hippocampal head on the right but loss of digitation on the left. The upper right image shows prominent dentation of the ventral surface of the hippocampus, but the lower right image shows minimal dentation.

B.05

INVASIVE MONITORING USING DEPTH ELECTRODES AT A NORTH AMERICAN CENTER: A PROSPECTIVE STUDY ANALYZING THE FEASIBILITY AND SAFETY OF STEREO-ELECTROENCEPHALOGRAPHY (SEEG) IN THE DIAGNOSIS AND TREATMENT OF INTRACTABLE EPILEPSY

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Rationale: Invasive monitoring using depth electrodes is relatively under-utilized in North America, where subdural grid/strip mapping is considered the method of choice in many centers. We report our experience at Cleveland Clinic with stereo-electroencephalography (SEEG) regarding its feasibility and safety in the diagnosis and treatment of intractable epilepsy.

Methods: We prospectively analyzed 55 patients who underwent SEEG implantation during the period of March 2009 to May 2010. The main goals for SEEG electrode implantation included (1) mapping of the epileptogenic zone and/or (2) definition of cortical function. Indications for SEEG included discordant pre-operative data, presumed proximity of the epileptogenic zone to eloquent areas in the brain, possibility of multifocal or bi-hemispheric epilepsy and failed previous subdural invasive mapping. Information regarding patient's demographics, success in the definition of the epileptogenic zone and surgical complications were prospectively analyzed.

Results: The mean age of the studied population was 30 years. The mean follow-up was 7 months after the invasive monitoring procedure. Mean duration of the epilepsy was 19 years. Twenty two patients had their epileptogenic zone located in the temporal lobes and 33 patients were considered extra-temporal. Twenty patients (36%) had normal MRIs. The total number of implanted electrodes was 703 with an average of 13 electrodes per patient. The SEEG method led to the localization of the epileptogenic zone in 51 patients (94%). From this group, 46 patients underwent resective surgery guided by SEEG (83.5%). Seven patients failed previous subdural grid implantation. SEEG localized the epileptogenic zone in all patients from this subgroup. In this highly complex group of patients, SEEG failed to localize the epileptogenic zone in 4 patients (diffuse seizure onset in most contacts and/or ictal semiology preceding SEEG ictal onset). Complication rate was 3%, corresponding to 2 patients with asymptomatic intracerebral hemorrhages. No permanent complications or mortality occurred.

Conclusions: The SEEG methodology demonstrated to be safe and efficient in mapping the epileptogenic zone. Long term seizure outcome is necessary to validate this method. Specific indications for SEEG as compared to subdural grid mapping will need further definition

B.06

PAUCITY OF HIPPOCAMPAL DIGITATIONS DETECTED BY 7 TESLA MRI IN TLE WITH HIPPOCAMPAL SCLEROSIS

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Rationale: Clinical 1.5 and 3 Tesla magnetic resonance imaging (MRI) often detects hippocampal sclerosis (HS) in mesial temporal lobe epilepsy (TLE). Focal hippocampal dysplasia associated with HS has been detected histopathologically in TLE surgical specimens. We hypothesized that 7 T MRI might detect hippocampal malformations with HS in TLE, with increased contrast and submillimetric spatial resolution.

Methods: We acquired T1- and T2-weighted 7 T brain MRI in 11 healthy subjects and 8 unilateral TLE patients, who consented with IRB approval. Patients had scalp EEG ictal onsets over one temporal lobe, which was ipsilateral to hippocampal atrophy or T2 increases on clinical MRI. T1-weighted, 3-dimensional, magnetization-prepared, rapid acquisition, gradient-recalled-echo (0.8x0.8x0.8mm3 resolution) sequences imaged the whole brain. T2-weighted, turbo spin echo (0.25x0.25x1.2 mm3) sequences imaged the entire hippocampus, in contiguous oblique coronal slices. Data were analyzed qualitatively to define morphology and count hippocampal head digitations.

Results: Each 7 T image set in healthy and TLE subjects showed submillimetric hippocampal shape and structures including the hippocampal striation (intrahippocampal white matter which separates Ammon's horn and dentate gyrus), and the alveus, on coronal images. Among 22 hippocampi in healthy subjects, one hippocampus had a single digitation and the others had 2-3 digitations of the hippocampal head. All TLE subjects had 0 or 1 hippocampal digitation on the

epileptogenic side, and 3 also had 0 or 1 digitation contralaterally. Malrotations of the hippocampal body were observed in 3 TLE and 4 healthy subjects. (Clinical MRI did not consistently detect the hippocampal striation, alveus, and other structures that were visible at 7 T. Clinical MRI did not consistently detect paucity of digitations, and malrotations, which were detected at 7 T.) The Figure shows T2-weighted coronal 7 T images through the hippocampal heads (upper two panels) and bodies (lower panel) in a healthy (c9) and TLE (p1) subject; black arrows indicate the hippocampal striation with normal digitations (c9) and bilaterally absent digitations (p1), and the white arrow indicates malrotation of the hippocampal body (contralateral to HS, in p1).

Conclusions: Ultrahigh field MR images defined internal and external hippocampal morphology more clearly than did clinical MRI. Hypoplasia of the hippocampal head may be highly associated with HS, but can occur contralateral to HS in TLE patients. Absence or paucity of digitations of the hippocampal head may represent a specific deformity of hippocampal morphology in mesial TLE. Histopathological correlation will be required to determine whether this deformity is an MRI sign of hippocampal dysplasia. Malrotation of the hippocampal body may be a normal variant of hippocampal morphology. Improved contrast and submillimetric spatial resolution at 7 T should considerably enhance future pathophysiological research and perhaps surgical planning in TLE.

Acknowledgments: Supported by NIH P41 RR008079 & P30 NS057091, and the Keck Foundation.

IMAGE: images/906998_A.jpg

B.07

SURGICAL OUTCOME IN SUBDURAL GRID BASED NEOCORTICAL EPILEPSY RESECTIONS

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Rationale: Neocortical epilepsy (NE) surgery is widely performed for severely intractable seizure disorders localized to lateral temporal and extratemporal locations. These surgeries require highly specialized costly evaluations, and nearly always require intracranial EEG (ICEEG) recordings. The American Academy of Neurology Practice Parameter Statement published in 2003 states that insufficient evidence exists to make a recommendation as to whether patients will or will not benefit from NE surgery. This work provides an estimate of long-term seizure-free outcome data specific to this very important subset of epilepsy surgery patients, and can be used in decision analysis of the clinical utility of NE surgery.

Methods: A retrospective review of all ICEEG based NE resections since 1996 at UAB was performed. An epilepsy nurse specialist (SM) obtained Engel class outcome assessments from telephone call interview or medical record review (when patients could not be reached). Outcomes were stratified according to MRI classification—negative (normal or questionable abnormality) and positive (localized, multiple, large or ambiguous abnormality).

Results: Of 115 NE patients that had ICEEG investigations at UAB since January 1996, 99 (86%) had surgical resections. Seventy-four patients (one lost to follow up) had one year or greater duration of follow up. The Table shows demographics, epilepsy class and post surgery outcome of these cases sorted by MRI negative (n=35) and MRI postive (n=39) classification. The independent variables were comparable between groups. The mean duration of follow up for assessment of seizure outcome was 4.8 years (range 1.3-13.8). The overall seizure free incidence (57% MRI negative and 54% MRI positive) was not significantly different between groups.

Conclusions: ICEEG based NE epilepsy surgery seizure-free outcomes for normal MRI cases are similar to those with abnormal MRI. Although predictors of outcome in NE remain unclear, overall effect on seizure-free outcome is robust. These data and others reported in the literature can be combined with cost and risk assessments in decision-making models to perform sensitivity analyses of all variables effecting whether patients should have NE surgery.

Table

IMAGE: tables/907229_T1.jpg

B.08

PHOSPHORUS MAGNETIC RESONANCE SPECTROSCOPY AT HIGH FIELD IN PATIENTS WITH MALFORMATIONS OF CORTICAL DEVELOPMENT

C. S. Andrade[1], M. C. Otaduy[1], D. F. Maia[2], K. Valente[2] and C. C. Leite[1] ([1]Magnetic Resonance Department, Institute of Radiology - University of São Paulo (USP), São Paulo, Brazil and [2]Laboratory of Clinical Neurophysiology, Institute of Psychiatry, University of São Paulo (USP), São Paulo, Brazil)

Rationale: Malformations of cortical development (MCD) is an important cause of epilepsy and the elucidation of pathophysiological basis may help to understand of human epileptogenesis. Some previous studies with MRS have demonstrated abnormal metabolites, indicating dysfuntions of neuronal nature in the cortex beyond the visible lesions. To the moment, there are no studies with phosphorus magnetic resonance spectroscopy (31P-MRS) in MCD. The purpose of this study is to evaluate phospholipids metabolism in patients with malformations of cortical development (MCD).

Methods: We have performed phosphorus magnetic resonance spectroscopy (31P-MRS) at high field in eight patients with MCD and in eight healthy volunteers. Pulse acquire sequence was applied with decoupling and a matrix of 6 slices, 7 columns and 8 lines with each voxel size of 25 x 25 x 20 mm. Individual voxels were selected in the focal lesions and in the contralateral normal appearing parenchyma (CNAP) of patients and in right and left cerebral hemispheres of controls (Figure 1). The amplitude values of each metabolite divided by the sum of all metabolites were obtained. The following metabolite peaks were identified: PE - phosphoril-etanolamine, PC - phosphoril-coline, Pi - inorganic phosphate, GPE - glicero-phosphoril-etanolamine, GPC - glicero-phosphoril-coline, PCr - phosphocreatine, g-, a- and b-ATP - adenosine triphosphate. We also calculated the total ATP, phosphodiesthers - PDE and phosphomonoesthers - PME.

Results: The PCr values were significantly higher in the lesions (0.1980 ± 0.0150) compared with control subjects (0.1789 ± 0.0203), p=0.03 (Table 1). We found a significant reduction in patients of GPC (0.1144 ± 0.0254 in lesions, 0.1186 ± 0.0158 in NACP, 0.1373 ± 0.0134 in controls, p=0.007 and 0.005, respectively) and PDE (0.1872

± 0.0309 in lesions, 0.1942 ± 0.0164 in NACP, 0.2166 ± 0.021, p=0.01 and 0.01, respectively). In the other hand, there was significantly increase of PME in lesions (0.1788 ± 0.0216) compared to controls (0.1612 ± 0.0194), p=0.05 and also a significantly increase of PE in NACP of patients (0.1357 ± 0.0199) compared to controls (0.1166 ± 0.0165), p= 0.02.

Conclusions: In excitable tissues, the PCr acts as an energy buffer. Increased energy consumption can lead to an observable decrease in PCr levels. Our hypothesis is that MCD present higher levels of PCr because they are less metabolically active. Moreover, we found significant reduction of GPC and PDE in patients compared to controls and significant increase in PE and PME in patients versus controls. This finding could indicate a deregulation in the membrane synthesis in MCD. To our knowledge, this is the first work that demonstrates this pattern of metabolic abnormality in MCD with an in vivo study.

IMAGE: images/907841_A.jpg

Figure 1 - Multivoxel Phosphorus Magnetic Resonance Spectroscopy (31P-MRS) in a patient with unilateral gray matter periventricular heterotopia (shown in the upper part) and the spectroscopic curve below. In the right lower part, the metabolites amplitudes are demonstrated.

IMAGE: images/907841_B.jpg

Table 1 - Differences of phosphocreatine between patients with malformations of cortical development and normal controls.

B.09

ORBITOFRONTAL THINNING IN ASSOCIATION WITH DEPRESSIVE SYMPTOMS IN PATIENTS WITH EXTRATEMPORAL PARTIAL EPILEPSY

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Rationale: The importance of recognizing, treating and understanding depression in patients with epilepsy is acknowledged but has yet to be translated into practice. Abnormalities in limbic structures in the medial temporal lobe occur in depressed patients with temporal lobe epilepsy (TLE), as well as in depressed patients without epilepsy. The neural correlates of depression in patients with other types of epilepsy has not been well studied. We utilized MRI morphometric assessment to identify cortical regions associated with depressive symptoms in patients with focal epilepsy whose seizure foci were located outside the medial temporal lobe. For comparison, patients with TLE and healthy controls were also studied.

Methods: 21 patients with extratemporal (ET) epilepsy (7 frontal or frontal-temporal; 6 parietal or parietal-occipital; 8 multifocal), 36 patients with TLE, and 45 normal controls (NC) completed a Beck Depression Inventory (BDI) and underwent a high-resolution research MRI.

Scanning was performed at either the NYU Center for Brain Imaging or UCSD Radiology Imaging Laboratory. Acquisition parameters were optimized for increased gray/white matter image contrast. Image processing and analysis utilized the FreeSurfer software package. Cortical thickness was measured using automated procedures that segment the cortex and measure distance between the pial surface and gray/white matter boundary. For each hemisphere, a general linear model estimated the effects of BDI score on cortical thickness at each vertex along the cortical surface. The correlation between BDI score and cortical thickness was assessed within and between each subject group (ET, TLE, NC). Results were mapped onto an average brain surface and thresholded at p<.0005

Results: In ET patients, BDI score correlated negatively with thickness of left lateral orbitofrontal cortex (L LOFC) and R precentral and temporo-parietal cortex. In a comparison between ET and TLE patients, the correlation between BDI and cortical thickness differed in L LOFC and L frontal pole; for both regions, the BDI-thickness correlation was negative in ET and positive in TLE. Figure 1 shows the correlation of L LOFC thickness and BDI score in ET and TLE patients, as well as healthy controls. There is a negative correlation between BDI and L LOFC thickness in ET patients and NC subjects, as compared to a positive correlation in TLE patients.

Conclusions: In patients with extratemporal partial epilepsy, as well as in healthy controls without epilepsy, increasing severity of depressive symptoms was associated with L LOFC thinning. In contrast, patients with TLE had L LOFC thickening in association with increased depression. The OFC is a brain region involved in emotional regulation and reward processing previously implicated in depression. These preliminary results suggest that the neural basis of depression in patients with extratemporal epilepsy is similar to that in people without epilepsy, while depression in TLE may be different.

IMAGE: images/907244_A.jpg

Monday, December 6, 2010

Platform Session C

4:00 p.m.-6:00 p.m.

C.01

OVER 10-30 YEARS OF FOLLOW UP, HOW OFTEN DO PEOPLE WITH CHILDHOOD-ONSET INTRACTABLE FOCAL EPILEPSY HAVE A SUBSTANTIAL BUT TEMPORARY REMISSION?

Carol S. Camfield and P. R. Camfield (Pediatrics, Dalhousie University and the IWK Health Centre, Halifax, NS, Canada)

Rationale: A large retrospective study of adults assessed for epilepsy surgery found that many had epilepsy onset in childhood with a significant remission followed by intractable epilepsy (Berg et al Ann Neurol. 2006;60:73-9). Our prospective study documents the frequency of this distressing sequence of events.

Methods: We selected patients from the Nova Scotia Childhood Population-based Cohort with symptomatic or cryptogenic partial epilepsy (SFE) and follow up e”10 years. Benign focal epilepsy syndromes were excluded. A significant remission was defined as e”1 year seizure free.

Results: Two groups of patients were analyzed: 1) all in the cohort with mental retardation and SFE, 2) a convenience sample (about 50% of those in the cohort) with normal intelligence and SFE.

Of the 51 with SFE and mental retardation, age of epilepsy onset averaged 5±4.3 years and average follow up was 22.2±4 years. At the end of follow up, average age was 26.6±4.8 years, when 13 (25%) had intractable epilepsy and one had successful epilepsy surgery. Only 3 had a significant remission, ranging from 1.5 to 4.8 years. The time from epilepsy onset to the beginning of the remission was 0.8 to 5.5 years. One patient attempted to discontinue AED treatment during remission. In each case remission was again followed by intractable epilepsy.

Of the 81 with normal intelligence and SFE, age of onset averaged 7.2±4.5 years and follow up averaged 26.9±4.9 years. Age at the end of follow up averaged 34±6.8 years. Eleven (14%) had epilepsy surgery of whom 6 had a significant remission prior to surgery lasting 1 year (n=1), 1-3 years (n=4) and 5 years (n=1). The interval between epilepsy onset and the start of remission was <1 year (n=2), 1.5-4.5 years (n=3) and 8 years (n=1). Three attempted to discontinue AED treatment during remission although intractable seizures returned promptly.

An additional 10 (12%) patients with normal intelligence and SFE developed intractable epilepsy but did not undergo surgery. Five had a significant remission lasting 1-2 years (n=4) and 5 years (n=1). The interval between onset of epilepsy and the start of remission was <1 year (n=1), 6 years (n=1), 10-13.4 years (n=4). Five had attempted to discontinue AED treatment during their remission.

Combining the groups, 35 of 132 (27%) had intractable epilepsy with/without epilepsy surgery. 69% of intractables had a significant but transient remission e”1 year although only 4 had a remission >4 years. Nine (26%) attempted to discontinue AED treatment during remission.

Conclusions: Over 10-30 years of follow up, about two thirds of children with intractable symptomatic or cryptogenic focal epilepsy will have a substantial but temporary remission. The remissions usually begin after a few years of active epilepsy and most are relatively short (< 2 years) but in ~25% are long enough to attempt discontinuing AED treatment. At least 5 years of remission is needed before children with intractable partial epilepsy can be nearly certain that their epilepsy has resolved.

C.02

LONG TERM FOLLOW-UP OF THE RNS(TM) SYSTEM IN ADULTS WITH MEDICALLY INTRACTABLE PARTIAL ONSET SEIZURES

C. N. Heck[1] and -. the RNS System Investigators[2] ([1]Neurology, USC, Los Angeles, CA and [2]N/A, N/A, CA)

Rationale: The RNS™ System (NeuroPace, Inc.) is an investigational device that includes a cranially implanted programmable responsive neurostimulator connected to depth and/or subdural leads, a physician programmer, a patient remote monitor and a web based interactive database. Long-term seizure frequency and responder rate, as well as safety, were assessed in subjects with medically intractable partial onset seizures participating in the RNS System studies.

Methods: Subjects were 18-70 years of age, had > 3 disabling partial seizures/month and had failed > 2 AEDs. After a 3 month baseline, the Neurostimulator and Leads were implanted and the neurostimulator was programmed to detect epileptiform activity. Subjects in a Pivotal study (N=191) were randomized 1:1 to receive active or sham responsive stimulation for 12 weeks, beginning 8 weeks post-operatively. Subjects in a Feasibility study (N=65) were able to receive responsive stimulation for 12 weeks beginning 4 weeks postoperatively, except for 14 subjects randomized to receive sham stimulation in a later blinded protocol. At the end of the evaluation period, all subjects could receive stimulation until 2 years post-implant, and then could transition into an ongoing 5 year, open label, long term treatment trial. Assessment variables included the seizure frequency % change and responder rate (percent of subjects with a 50% or greater reduction in seizures) for each 6-month interval beginning 6 months after implant (when all subjects have the opportunity to receive stimulation). Safety of responsive stimulation was assessed by adverse event reporting.

Results: 256 subjects were implanted with the RNS Neurostimulator and Leads. The mean age at enrollment was 34.0 years, mean duration of epilepsy was 19.6 years, mean number of AEDs was 2.9, and median seizure frequency was 10.1 seizures/28 days. The responder rate and the median percent reduction in frequency of total disabling seizures for each 6 month interval is presented in Table 1, with the number of subjects currently reaching that time point. There were no serious unanticipated device-related adverse events during the RNS(TM) System studies, and the overall rate of adverse events did not increase over time.

Conclusions: Seizure frequency was reduced across subjects participating in clinical studies of the RNS System. After 2 years post-implant (2 - 2.5 yrs), the median % seizure reduction was >40% and the responder rate was >45%. After 3 years (3 - 3.5 yrs) 53% were responders. These data suggest that the reduction of the seizure frequency is maintained with responsive stimulation, and appears to improve over time. Adverse event rates were stable, supporting the safety of responsive stimulation over time.

Responder rates and seizure frequency percent change over time

IMAGE: tables/907013_T1.jpg

N is the number of subjects for whom any data were available during the specified interval

C.03

COMBINED ANALYSIS OF RISK FACTORS FOR SUDEP

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Rationale: Sudden unexpected death in epilepsy (SUDEP) is the most common condition-related cause of death in chronic epilepsy. Case-control studies using living people with epilepsy as controls have aimed at identifying factors that distinguish the epilepsy patient at risk for SUDEP. Patient demographics, seizure and epilepsy characteristics, comorbidities, and treatment with AEDs have thus to a variable extent been analyzed as risk factors in these studies. Some risk factors, e.g. high frequency of generalized tonic-clonic seizures (GTCS), have been consistently identified. There are also disagreements between the studies and a lack of precision in the risk estimates, which can be attributed to small number of cases in each study. To counteract these limitations, the Epidemiology task force of the International League Against Epilepsy pooled data from the four published case-control studies of sudden unexplained death in epilepsy (SUDEP) with live controls, to increase the power to determine risk factors.

Methods: Case-control studies from the US, Sweden, Scotland and England were combined. SUDEP was defined as 1) a history of epilepsy (> 1 epileptic seizure during a period of <5 years); 2) death occurring suddenly; 3) death unexpected (i.e., no life threatening illness); and 4) death remained unexplained after all investigative efforts, including autopsy. Definite SUDEP required all criteria. Logistic regression analyses adjusted for study. Further analysis simultaneously adjusted for study, age at death, gender, and duration of epilepsy.

Results: Statistically significant SUDEP risk factors (Table 1) included increased frequency of generalized tonic clonic seizures (GTCS), use of polytherapy, duration of epilepsy, young age at onset, gender, symptomatic etiology, and lamotrigine therapy. Results persisted when epilepsy onset was younger than 16 years and when it was 16 years or older. In univariate analysis, lamotrigine therapy was associated with significantly increased risk for SUDEP among individuals with idiopathic generalized epilepsy.

Conclusions: This analysis refines the identification of people with epilepsy that are at particular risk of SUDEP. The emerging profile indicates that people with early onset refractory symptomatic epilepsy with frequent GTCS and antiepileptic drug (AED) polytherapy are at higher risk. The results suggest that reduction of the number of GTCS is a priority, of more importance than reducing the number of AEDs. The role of AEDs and other treatment should be analyzed further in future studies.

Funded by The International League Against Epilepsy

Table 1. Results of logistic regression analyses examining associations between risk factors and SUDEP across multiple data sources

IMAGE: tables/905801_T1.jpg

[1] Adjusted for data source

[2] Adjusted for data source, gender, age at death, and duration of epilepsy

[3] Includes information from all data sources with England as referent data source

[4] Includes information from England, Minnesota, and Sweden with England as referent data source

[5] Includes information from England, US, and Scotland with England as referent data source

[6] Includes information from England and Scotland with England as referent data source

C.04

UNCONTROLLED EPILEPSY IN A MEDICAID POPULATION

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Rationale: The purpose of this study is to evaluate the clinical and economic burden of uncontrolled epilepsy when compared to controlled epilepsy in a Medicaid population.

Methods: Medical and pharmacy claims from Florida (1997Q3-2008Q2), Iowa (1998Q1-2006Q2), Kansas (2001Q1-2009Q2), Missouri (1997Q1-2008Q2), and New Jersey (1997Q1-2008Q4) Medicaid databases were analyzed. Patient selection criteria were: e" 18 years old; e" 1 medical visit with e" 1 diagnosis of epilepsy (ICD-9 345.xx) or e" 2 diagnoses of non-febrile convulsions (ICD-9 780.3 or 780.39) occurring e" 30 days apart; e" 1 pharmacy dispensing of any AED; and continuous enrollment throughout observation (minimum 365 days). A retrospective longitudinal matched-cohort design was used to classify patients into mutually-exclusive cohorts of "uncontrolled", "intermediate", and "well-controlled" epilepsy. Uncontrolled epilepsy was defined as e" 2 consecutive changes in AED therapy occurring e" 30 days apart, followed by e" 1 epilepsy-related inpatient or ER visit within the next 365 days. Well-controlled epilepsy was defined as no AED change, and no epilepsy-related inpatient or ER visit. Patients not uncontrolled or well-controlled were classified in the intermediate group. Patients of the well-controlled and intermediate groups were matched 1:1, respectively, with those with uncontrolled epilepsy using propensity score matching. Matched cohorts were compared for resource use, and occurrence of negative clinical events. Statistical differences between cohorts were assessed using multivariate regression models, adjusted for demographics, treatment characteristics, and comorbidities.

Results: From 110,425 eligible patients with epilepsy, 3,562 patients (mean age=41.4, 38.9% male) with uncontrolled epilepsy were identified. In total, 3,318 well-controlled and 3,560 intermediate patients were matched 1:1 with uncontrolled epilepsy patients. Compared to well-controlled epilepsy, patients with uncontrolled epilepsy had significantly higher all-cause hospitalizations rates (1.4 vs. 0.2 visits/patient-year, adjusted rate ratio [ARR]=6.99, p<.001), longer hospital stays (9.7 vs. 1.5 days/patient-year, ARR=6.76, p<.001), more frequent emergency-room visits (4.1 vs. 1.1 visits/patient-year, ARR=4.05, p<.001), and more neurologist visits (0.7 vs. 0.2 visits/patient-year, ARR=3.08, p<.001). Negative clinical events occurred more frequently in the uncontrolled epilepsy group (ARRs: fractures: 1.97, motor vehicle accident-related injuries: 2.89, head injuries: 1.89, and status epilepticus events: 38.43; p-values<.001) relative to well-controlled patients. Similar findings were observed between uncontrolled versus intermediate groups. Adjusted differences in pharmacy and medical costs will also be presented.

Conclusions: Uncontrolled epilepsy was associated with significantly greater healthcare resource utilization, and higher rates of negative outcomes compared to well-controlled epilepsy.

C.05

CONTINUOUS EEG MONITORING IN PEDIATRIC MODERATE-SEVERE TRAUMATIC BRAIN INJURY

Daniel Arndt, M. Tripputi and A. Brooks-Kayal (Pediatric Neurology, The Children's Hospital - University of Colorado - Denver, Aurora, CO)

Rationale: Traumatic Brain Injury (TBI) is the #1 cause of death and disability in the pediatric population. Early post-traumatic seizure (EPTS; seizure <7 days post-injury) is a frequent complication of pediatric moderate-severe TBI. The significance of continuous EEG (cEEG) monitoring has been shown in adult moderate-severe TBI, however, reports on cEEG in pediatric moderate-severe TBI are lacking.

Methods: 2 primary objectives were identified: (1) Define EPTS incidence/types in pediatric moderate-severe TBI relative to published adult rates; and (2) Determine if EPTS influence short-term outcome. We hypothesized that (1) children would have a higher rate of EPTS, electrographic-only EPTS, and epileptiform discharges (non-seizure group); and (2) EPTS negatively impact short-term outcome with longer ICU/hospital length of stay (LOS) and intubation, and worse global outcome.

27 patients with moderate-severe TBI consecutively admitted over 9 months, who received institution-wide TBI-specific cEEG protocol reviewed by epileptologists, were consented and enrolled; only 1 patient was ineligible (no cEEG). 25 gold electrodes were placed by the International 10-20 system. Seizures were typed as clinical (clinically apparent signs during electrographic seizure), subtle clinical (clinical signs only detectable on careful video review of EEG-detected seizure), and electrographic (no clinical signs); "subclinical" includes both subtle clinical and electrographic types. KOSCHI outcomes were dichotomized (Good = 4-5, Bad = 1-3). Chi square, t-tests, and logistic regression analyses were used.

Results: See table 1 for data summary and comparison with adults (Vespa et al. '99), by +/- EPTS groups, and by mechanism of injury (M.O.I.). Figure 1 outlines time to first EPTS and EPTS incidence by M.O.I. EPTS rate (both prior to and during cEEG) was 2.5-fold higher than adult rate (55.5% vs 22.3%; p=0.03), and even higher in nonaccidental trauma (NAT, 84.6%, p=0.01). 10/15 with EPTS (67%), or 10/27 (37%) total patients recorded, had subclinical seizures detected only by cEEG (mostly electrographic-only). Electrographic-only EPTS rate (no clinical signs, 3/27, 11.1%) was similar to adults (11.7%; p>0.99). Epileptiform discharge rate (non-seizure group) was 5-fold higher than adults (50% vs 10%; p=0.02). Status epilepticus occurred <7 days post-injury in 12/27 (44.4%), and was often subclinical (8/12, 67%). EPTS risk was significantly increased with both NAT (RR 2.96, p=0.007) and age <2yo (RR 3.7, p=0.003). NAT risk remained significant after adjustment for post-injury hypotension/hypoxia (RR 2.94, p=0.01).

Conclusions: Children had significantly higher EPTS and epileptiform discharge rates than adults. Children have high rates of subclinical EPTS and status epilepticus detected only by cEEG. EPTS rates were significantly higher and occurred earlier in NAT children. Age <2yo was also a predictor of EPTS, and it is unclear if mechanism of injury or younger age, or both, were critical factors. EPTS did not influence any short-term outcome measures.

IMAGE: images/904536_A.jpg

Table 1. Data summary and comparison with adults, by presence or absence of early post-traumatic seizure (EPTS), and by mechanism of injury (MOI).

IMAGE: images/904536_B.jpg

Figure 1. Time to first early post-traumatic seizures (EPTS) and incidence by mechanism of injury (MOI).

C.06

MORTALITY IN EPILEPSY - RESULTS FROM A LARGE DANISH COHORT

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Rationale: Studies have reported excess mortality associated with epilepsy, but the precise contribution of the underlying conditions is unknown.

Methods: We evaluated a cohort of children born in Denmark from January 1 1977 to December 31, 2006 by linking information from registries for civil service, health and cause of death. Children were followed from the 29th day of life until death emigration or December 31, 2006. We estimated the overall and cause-specific mortality after first admission with epilepsy.

Results: Overall, 10,648 people died during 26.2 million person years of follow up. Of the people who died, 806 were diagnosed with epilepsy prior to death. The overall mortality rate ratio (MRR) was 14.63 (95% CI: 13.57-15.76). The risk was increased even after excluding children with adverse birth outcomes (birth weight < 2,500 g, Apgar Score <10, and gestational age < 37 weeks) (MRR: 10.65 (95% CI: 9.50 - 11.89)). The MRR was particular high for both genders the first five years of life and shortly after onset of epilepsy.

Conclusions: People with epilepsy had a highly increased MRR. The mortality rate was extremely high shortly after onset with epilepsy and for people with early onset of epilepsy. The increased mortality rate was only partially explained by adverse birth outcomes.

C.07

COGNITIVE FUNCTIONS AT AGE 4.5 YEARS IN CHILDREN EXPOSED IN UTERO TO ANTIEPILEPTIC DRUG

Kimford J. Meador[1], G. A. Baker[2], N. Browning[3], J. Clayton-Smith[4], M. Cohen[5], T. Crawford[3], L. Kalayjian[6], A. Kanner[7], J. Liporace[8], P. Pennell[9], M. Privitera[10], D. Loring[1] and A. NEAD Study Group[1] ([1]Neurology, Emory University, Atlanta, GA; [2]Neurological Science, University of Liverpool, Merseyside, United Kingdom; [3]EMMES Corporation, Rockville, MD; [4]University of Manchester, Manchester, United Kingdom; [5]Neurology, Medical College of Georgia, Augusta, GA; [6]Neurology, University of Southern California, Los Angeles, CA; [7]Neurology, Rush University Medical Center, Chicago, IL; [8]Center for Neuroscience, Media, PA; [9]Neurology, Harvard University, Boston, MA and [10]Neurology, University of Cincinnati, Cincinnati, OH)

Rationale: Previously, we reported that fetal exposure to valproate impairs IQ at age 3 years (Meador et al. NEJM 2009). Here, we extend our findings by examining the effects of fetal antiepileptic drug (AED) exposure on IQ at age 4.5 years.

Methods: The NEAD Study is an ongoing prospective observational multicenter study in the USA and UK, which enrolled pregnant women with epilepsy on AED monotherapy from 1999 to 2004. The purpose of the investigation is to determine if differential long-term neurodevelopmental effects exist across four commonly used AEDs (carbamazepine, lamotrigine, phenytoin, or valproate). The primary outcome is IQ at age 6 years. This planned interim analysis reports on IQ at age 4.5 in 209 children as measured by the Differential Ability Scale.

Results: In a multivariate analysis with age 4.5 IQ as outcome, significant effects were found for AED group (p=.04; child IQ lower with valproate exposure), maternal IQ (p<.001; child IQ higher with

higher maternal IQ), maternal education (p=.007; child IQ higher with higher maternal education), maternal age (p=.004; child IQ lower in youngest mothers), gestational age (p=.02; child IQ lower with lower gestational age), race (p=.008; child IQ higher in Caucasians), and alcohol use during pregnancy (p=.007; child IQ lower with alcohol exposure). IQ was negatively associated with valproate dose (r=-.33, p=.04), but associations for the other AEDs were not significant. Maternal IQ was associated with child IQ for children exposed to carbamazepine (r=.57, p<.001), lamotrigine (r=.35, p=.003), and phenytoin (r=.56, p<.001), but not valproate.

Conclusions: The differential adverse cognitive effects of fetal valproate exposure persist at this later age. Further research is needed to determine if these effects persist at older ages, and to determine effects of other AEDs.

C.08

HIPPOCAMPAL GROWTH IN CHILDREN IS NOT AFFECTED BY PROLONGED SEIZURES

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Rationale: After an episode of Convulsive Status Epilepticus (CSE) there is understandable concern about the harm that prolonged seizures may do to the developing brain. There is a known association between prolonged febrile seizures (PFS) and the subsequent development of mesial temporal sclerosis (MTS). Brain imaging following PFS has shown signs suggestive of acute hippocampal injury. Our longitudinal, prospective study of childhood CSE is the first to investigate the evolution of hippocampal changes and whether they are specific to PFS.

Methods: Children with CSE were recruited from London hospitals and detailed clinical and demographic data collected. MRI investigations were performed in a Seimens Avanto 1.5T scanner at 1, 4 and 12 months after the episode of CSE, including a T1 weighted three-dimensional fast low angle shot (3D-FLASH), which was used to derive the hippocampal volume (HV).

HV was measured by tracing consecutive coronal slices with simultaneous reference to a visualisation in 3 orthogonal planes using the 3D-FLASH dataset. Brain volume (BV) was measured by using automated software (BET - FSL) to strip the skull and surrounding soft tissue with manual correction as necessary.

Each patient was assigned to an aetiological group based on their initial clinical history and examination.

Controls with no previous seizures and no neurological abnormalities were also enrolled.

Data was analysed in PASW 18.0 (Chicago, Illinois) for Windows using univariate ANOVA to compare groups and linear regression to model hippocampal growth against age and BV.

Results: 67 patient and 19 controls were available for analysis with at least one MRI brain scan. Full demographic details are available in Table 1. None of the children developed clinical MTS during this study.

After adjusting for age and BV, mean hippocampal volume 1 month after CSE was significantly related to brain volume ($p < 0.001$), age ($p=0.035$), and aetiology ($p =0.011$). Children with symptomatic CSE had a 206 mm3 (43-369) smaller mean HV ($p=0.014$) than controls. All other groups did not differ significantly from controls.

In order to compare hippocampal growth over time, a model of predicted hippocampal volume was constructed. There was no significant difference in growth rates between the groups at 4 months or at 1 year.

Conclusions: We found no evidence of long term hippocampal injury in children following an episode of CSE. In particular, any hippocampal swelling that occurs immediately following a PFS has resolved at 1 month and does not have a long term effect on hippocampal growth. This suggests that the risk of progression to MTS is low.

Mean HV at 1 month is reduced in children with symptomatic CSE. As these children also had a range of other structural brain abnormalities, this is likely to be only one element of a wider brain disorder.

Our study suggests that long term hippocampal injury in previously normal children after CSE is uncommon. Further analysis of our cohort will enable us to ascertain whether there is a subgroup of children who may show signs of long term hippocampal injury and any particular risk factors for this.

IMAGE: tables/898080_T1.jpg

Table 1: Demographic details of patients and controls

C.09

LATERALIZATION OF TEMPORAL LOBE EPILEPSY WITH LONG-TERM AMBULATORY INTRACRANIAL MONITORING USING THE RNS™ SYSTEM: EXPERIENCE AT 4 CENTERS

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Rationale: We present the results of long-term ambulatory electrocorticography (ECoG) from 22 subjects with localization related epilepsy of temporal lobe onset (TLE) who were studied with bilateral hippocampal (Hc) depth electrodes while participating in a trial of the RNS™ System (NeuroPace) cranially implanted responsive neurostimulator. The intent was to determine the distribution of left and right Hc onsets, as well as the length of time that seizures were detected from one Hc before being detected in the other.

Methods: All subjects had been diagnosed with TLE of Hc origin and were participating in an investigational trial of the RNS™ System at 4 centers. Four-contact depth leads were stereotactically implanted along the longitudinal axis of each Hc. ECoGs were stored by the neurostimulator based on detected electrographic seizures and then uploaded to a secure data management system. Electrographic seizures were defined as episodes of low-voltage fast-activity or rhythmic sharp activity, distinct from background, detected for longer than 25 seconds. The data was collected post-implant, prior to receiving neurostimulation. Medications remained stable during the data collection period. An analysis was performed of the side of ictal onset

as well as the longest interval before onsets switched from one Hc to the other (longest interval before switching (LIBS)).

Results: Subjects were between 21 and 52 years of age. All had failed at least 5 antiepileptic drugs and 7 had failed VNS therapy. Fourteen (14) subjects had presumed bilateral mesial temporal onsets from either scalp or intracranial monitoring. Eight (8) subjects had unilateral mesial temporal onsets on scalp or intracranial EEG but were not candidates for temporal lobectomy because there was bilateral Hc atrophy (2), onsets contralateral to the Hc atrophy (1), failed WADA testing (2) or onsets from the dominant temporal lobe with PET abnormality from the contralateral side (1) or failed dominant lobe resection (2).

Temporal lobe lateralization, MRI results, length ECoG data collection, number and lateralization of Hc seizure onsets recorded by the RNS™ System and number of days before onsets switched from one Hc to the other (LIBS) are presented in the table.

Conclusions: Twenty-two (22) subjects with TLE of Hc origin underwent long-term intracranial ambulatory ECoG monitoring while participating in the RNS™ System investigational trial. Three (3) subjects with presumed left lateralization had bilateral onsets. In the 15 subjects with bilateral independent Hc onsets, seizures were lateralized solely to one Hc for an average of 16 days (4 - 39 days) before onsets were recorded in the contralateral Hc. This suggests that many days of EEG monitoring with scalp or intracranial electrodes may be required in order to confidently lateralize epilepsy of Hc origin.

IMAGE: tables/904902_T1.jpg

Monday, December 6, 2010

Pediatric State of the Art Symposium - Identifying and Managing the Comorbidities of Pediatric Epilepsy

6:30 p.m.-8:30 p.m.

PL.02

IDENTIFYING AND MANAGING THE COMORBIDITIES OF PEDIATRIC EPILEPSY

Madison Berl[1] and Joseph Sullivan[2] ([1]Neuroscience, Children's National Medical Center, Washington, DC and [2]Neurology, University of California San Francisco, San Francisco, CA)

Summary: Children with epilepsy have an increased risk of neuropsychological and neuropsychiatric impairments that may predate seizure onset and can persist—even after seizures are medically controlled—into adulthood, and thus are arguably more impairing than seizures themselves. The comorbidities of pediatric epilepsy have historically been understudied resulting in limited understanding of the scope and specifics of the impairments. Moreover, insufficient availability of mental health providers makes referrals difficult to find or delayed in taking place, obliging the epilepsy clinician to manage the comorbidities in the meantime. This symposium will characterize the cognitive phenotypes of pediatric epilepsy (beyond IQ), delineate the range and prevalence of psychiatric disorders, and provide practical recommendations for the clinician based on recent neuroimaging and outcome studies. Practical guidance includes knowing what questions to ask to screen for disorders and make a plan to provide optimal care, making decisions regarding pharmacological treatment, and providing immediate, home-based recommendations.

Tuesday, December 7, 2010

Plenary II: Neurostimulation in the Treatment of Epilepsy: The Road Traveled and the Road Ahead
9:00 a.m.-10:30 a.m.

PL.03

NEUROSTIMULATION IN THE TREATMENT OF EPILEPSY: THE ROAD TRAVELED AND THE ROAD AHEAD

Gregory K. Bergey (Johns Hopkins University School of Medicine, Baltimore, MD)

Summary: Despite the introduction of a large number of new AEDs in recent years, the number of patients with seizures that are refractory to medical therapy has not been significantly reduced. This has prompted renewed interest in studies of therapy with neurostimulation. Neurostimulation for the treatment of epilepsy has the benefits of no drug related side effects and mechanisms of action presumed to be distinct from antiepileptic drugs, although the actual mechanisms of action are not established. Following the approval in 1997 of vagus nerve stimulation for adjunctive treatment of partial seizures, more recent trials have targeted intracranial sites. Two pivotal multicenter trials have recently been completed and submitted to the FDA for review. One trial employs programmed stimulation of the anterior thalamus. The other trial utilizes responsive stimulation where intracranial electrodes placed near the seizure focus are programmed to detect seizure activity early and to deliver a stimulus to hopefully disrupt or terminate the seizure. Both trials have demonstrated significant efficacy during the early double blind periods. Unlike antiepileptic drug trials where dose and side effects are the important and definable criteria, neurostimulation, whether programmed or responsive, involves parameters that are much less easily established. Stimulus frequency, intensity, and proximity to the seizure focus are just some of these considerations. In addition, optimization of the benefits of neurostimulation appears to occur only after a period of time, suggesting that some type of neuromodulation may play a role. This symposium will focus on the principles of neurostimulation, the different types of therapy, the results of the clinical trials, and the questions that remain for the optimal application of these novel therapies.

3.367

GI PROTEIN ACTIVATION AND D2-LIKE DOPAMINERGIC RECEPTOR BINDING IN A TEMPORAL LOBE EPILEPSY MODEL

Alcantara-Gonzalez D 1, Florán B 2, Rocha L 1

Objective: In the present study we investigated the alterations in D2-like dopamine receptor binding and the activation of Gi protein that is coupled to these receptors in an experimental model of epilepsy. *Methods:* In male Wistar rats used as control and "kindled" (epileptic) group (n=8, each), it was evaluated D2-like dopaminergic receptor binding and [35S]·GTP³S incorporation due to activation of D2-like receptors in different brain areas associated with epileptic activity, ipsi- and contralateral to the epileptic focus.

Results: It was observed a reduction in the D2-like dopaminergic receptor binding in striatum (25 and 35 %, ipsi- and contralateral) and contralateral nucleus accumbens (39 %) in "kindled" animals. However, there was an increase in the activation to Gi protein associated to D2-like dopaminergic receptor in striatum (91-121%); nucleus accumbens (88-112%); amygdala (46- 62%); entorhinal (52%), temporal (51-62%) and sensorimotor cortex (54-78%); sustantia nigra (31%), dorsal (56%) and ventral CA1 (30-34 %), ventral CA2 (63 %), ventral CA3 (30 %) and ventral dentate gyrus (25-28 %).

Conclusion. Despite there is a decrease in the D2-like dopaminergic receptor binding, it exist an increase in the activation of Gi protein coupled to these receptors. These results suggest a hypersensitivity to Dopamine effects mediated by D2-like dopamine receptors in the epileptic brain. ////

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3.368

METABOLIC ACTIVITY TEST USING FUNCTIONAL MAGNETIC RESONANCE WITH TEMPORAL LOBE EPILEPSY PATIENTS DURING THE STROOP TEST

[1]Jaqueline Alvarez-Alamilla, [1]María Corsi Cabrera, [2]Trejo Martínez D, [1]Irma Y del Río P, [2]Ana L Velasco M. ([1]Laboratory for Sleep Research, Postgraduate, Faculty of Pshychology, National Autonomous University of México. [2]Epilepsy Clinic, General Hospital of México.)

Rationale: Studies of patients with temporal lobe epilepsy had shown difficulties in processes regulated by the prefrontal cortex, and it had shown that this area is affected by its direct connection with medial areas such as the parahippocampal cortex and hippocampus (Simons and Spiers. Nat Rev Neurosci 2003; 4: 637-648). It results very important to evaluate the frontal and temporal lobe interaction because executive functions are regulated by them, and they are necessary for the daily life are necessary for the daily life. To evaluate the execution and the metabolic activation during the Stroop test in Temporal Lobe Epilepsy patients. Methods: Temporal lobe epilepsy patients, resistant to pharmacological treatment had been evaluated in three groups according to their epilepsy laterality: left (3), right (3) and bilateral (4). They were tested with the Stroop test, that consists naming the ink color in which the word is written, but with the name of another color (i.e., the word "green" is written with red color). This test was programmed in the E-Prime 1.1 software that let us register the reaction time and the type of responses. This test was evaluated in Functional Magnetic Resonance with the BOLD technique (Blood Oxygen Level Dependent) and it was analyzed through Matlab 7 and SPS 2 software. (Rajah MN. et al, Brain 2005; 128:1964-1983). Results: In left focus patients it has been found an activation prevalence on 10, 9, 39 and 40 Brodmann's areas and bilateral cerebellum; in right focus patients, 10 and 11 areas, and right cerebellum hemisphere; and in bilateral patients, 9, 7, 17 and 18 areas and right cerebellum hemisphere. Left patients obtained lower reaction times and more mistakes than right and bilateral patients. Conclusions: It has been found difference in the metabolic activation of different functional areas between groups as well as the reaction times for the test Stroop performance. In metabolic activation, patients with left and bilateral epilepsy showed more activation and involvement of anterior and posterior areas than right patients, which might suggests that patients with right focus may be more involved in networks that make us infer that these patients have a greater cognitive reserve, compared with patients with epilepsy right showed a lower metabolic demand. Study partially funded by DGAPA UNAM, IN228409.

3.369

FACTORS RELATED TO REFRACTORY EPILEPSY IN CHILDREN: "FEDERICO GOMEZ" CHILDREN´S HOSPITAL. EXPERIENCE IN MEXICO CITY

Arellano Montellano Ek Ixel, Barragán Pérez Eduardo. (Child Neurology Deparment. Hospital Infantil de México.)

INTRODUCTION: Epilepsy is one of the most common chronic neurological disorders, affecting more than 50 million people worldwide. More than 80 per 100 000 people develop new-onset epilepsy every year, most commonly during childhood and in old age. 50–60% of adults and children are expected to achieve seizure remission with medical management. However, 30—40% of patients remain refractory to pharmacological treatment. Epilepsy is associated with cognitive deterioration, psychosocial and family dysfunction, increased morbidity and mortality, expensive treatments, and poor quality of life. Early recognition of refractory epilepsy could potentially ameliorate these adverse consequences. Factors associated with refractory epilepsy are onset during the first year of life, type of epilepsy, failure of first antiepileptic drug (AED) within the first 6 months of therapy, temporal location of the epileptogenic focus, underlying brain damage, and specific EEG patterns.

OBJECTIVE: To identify factors related to the development of refractory epilepsy in pediatric patients with epilepsy at The "Federico Gómez" Children´s Hospital in Mexico City.

METHODS: Observational, descriptive, retrospective study.

INCLUSION CRITERIA. Outpatient with refractory epilepsy, ages 1 day to 16 years, seen in the Department of Neurology from January 2000 to December 2009 with complete medical records.

EXCLUSION CRITERIA. Patients with incomplete medical records. Data are presented using descriptive statistics.

RESULTS: 176 cases included in the study, and 49 patients met the criteria of refractory epilepsy, 49% female patients and 51% male patients. Two patients had Apgar score under 5, 4 scores of 6-8, 8 patients did not cry or breathe at birth (n = 14) and the remaining patients had Apgar scores above 8 or had no problems at birth (n = 35.)

The onset of seizures occurred more frequently from 1 to 12 months. The predominant type of initial seizure was infantile spasms.

The etiology of epilepsy was idiopathic in 1 patient, cryptogenic in 8 and symptomatic in 40 (81%).

Most of these patients had an abnormal neuroimaging, predominantly malformations (most commonly pachygyria, polymicrogyria, focal cortical dysplasia and digenesis of the corpus callosum).

DISCUSSION: Most patients present with poorly controlled epilepsy rather than refractory epilepsy as part of socio-environmental background rather than biological.

The incidence of perinatal asphyxia as a cause of refractory epilepsy was much lower than previously reported in Mexico. It may indicate improvement of pregnancy care and better conditions at birth in our country in recent years.

Like in previous studies, age at onset of seizures was one of the most important factors related to refractory epilepsy. We hypothesize that an early brain insult may be complicated by developmental epileptogenesis. Perhaps due to an early injury that lasts for the rest of the development of the individual. The cause of epilepsy in most cases was known and secondary to cerebral dysgenesis (most commonly pachygyria and polymicrogyria). These finding may be related to the widespread use of neuroimagin techniques in recent years.

CONCLUSIONS: Refractory epilepsy can be devastating to individuals and families. Evidence suggests that the response to treatment by patients is determined by genetic and environmental factors. MRI provides a useful tool in early diagnosis of cerebral dysgenesis. Early identification of refractory epilepsy may direct a more aggressive AED treatment or epilepsy surgery. Ultimately it may positively impact patients´ quality of life and clinical outcome.

3.370

CHARACTERISTICS OF PATIENTS WITH FIRST SEIZURE

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Introduction: 150,000 adults have a first seizure a year, of which 40 to 50% develop epilepsy. Seizures are triggered by epilepsy, tumors, and stroke, and vasculitis, metabolic or infectious diseases. Is essential a complete medical history, clinical examination and screening studies for the differential diagnosis.

Objectives: To describe the epidemiology, clinical and screening studies of adults with a first seizure.

Method: 1-year retrospective study that compiled demographic, clinical and screening studies for these patients.

Results: 24 patients, 60% female, mean age 41 ± 18 years. Background: cardiovascular diseases (25%), Diabetes mellitus (21%), head trauma (17%), alcoholism (17%), Eritematous Systemic Lupus (12%), renal failure (8%), syncope (4%) and family history of epilepsy (3%). Nobody had history of febrile seizures. Generalized seizures occurred in 54%. Seizures duration: 3.6 ± 2 min. One patient had status epilepticus (SE). Clinical manifestations: motor (67%), unresponsiveness (46%), sensory (17%), loss of consciousness (8%), psychiatric (8%), dizziness 8% and blurred vision (4%). The neurological examination was abnormal in 29%: 17% had manifestations of Parkinson disease, Stroke or peripheral neuropathy. The etiology was: symptomatic remote (46%), symptomatic acute (37%) and cryptogenic (17%)]. Etiology of symptomatic remote was: Stroke (25%), neuroinfections 12% (Toxoplasmosis, neurocysticercosis and meningoencephalitis), systemic infections (4%), neuroglial cyst (4%), vascular malformation (4%), cerebral hemorrhage (4%), brain abscess (4%) and vasculitis (4%). The imaging study (IS) was performed in 96% 74% was abnormal: focal lesions (56%), diffuse lesions (13%) and unspecified (4%). The EEG was abnormal in 67%: focal epileptiform activity (33%), generalized slowing (16%), focal slowing (12%) and nonspecific findings (4%). Discussion and conclusion: There were more seizures in middle-aged woman. The main backgrounds were: chronic degenerative diseases, head trauma and alcoholism. Family history of epilepsy was low. Generalized seizures lasting < 5 min were predominant. The main manifestations were motor and unresponsiveness. Most were symptomatic possibly because our hospital is a reference center, and the main origins were stroke and neuroinfections. Neurological examination was abnormal in 33%. The incidence of SE was low. Abnormalities in IS were higher when compared to 10% reported in literature. The main abnormality was focal lesion. EEG presented a high percentage of abnormalities compared to 23% reported by other authors and the main activity was the focal epileptiform.

3.371

EVALUATION OF 5-HT1A RECEPTOR IN THE HIPPOCAMPUS OF PATIENTS WITH REFRACTORY EPILEPSY TO ANTIEPILEPTIC DRUGS

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Rationale: Serotonin (5-hydroxytryptamine, 5-HT) has been involved in many cerebral disorders including epilepsy. Previous studies with PET reported decreased temporal 5-HT1A binding ipsilateral to seizure foci in patients with temporal lobe epilepsy (TLE) (Toczek et al. Neurology 2003; 60:749-756). However, hitherto little is known about studies on the binding properties of the 5-HT1A receptor in epileptic hippocampus tissue of patients with pharmacoresistant TLE. In this study, we characterize the 5-HT1A receptor binding as well as Gprotein activation mediated by these receptors in epileptic hippocampus of patients with pharmacoresistant. Methods: We obtained hippocampus tissue from 8 patients with TLE and brain tissue (hippocampus) of 5 autopsies from subjects who died from other causes different to neurological disease (Protocol approved by the scientific committee of the Hospital General of Mexico, DI/08/203/04/055). Competition binding experiments were performed using [3H]8-OHDPAT (1 nM) to evaluate the binding and IC50 (concentration required to inhibit 50% to receptor). Binding assays of [35S]GTP³S (0.05 nM) performed to evaluated the G-protein activation (Emax, expressed as % of stimulation of [35S]GTP³S).

Results: In contrast with autopsy samples (Emax= 74%), hippocampus obtained from patients with pharmacoresistant TLE demonstrated lower (Emax= 29%, $p<0.05$) 8-OH-DPAT-stimulated [35S]GTP³S binding. Competition binding experiments revealed that both groups demonstrated similar binding (38.7 ± 6.4 and 47.2 ± 10.8 fmol/mg of

protein, autopsy and TLE, respectively) and IC50 (1.2 ± 0.21 and 0.83 ± 0.12 nM, autopsy and TLE, respectively) values.

Conclusions: Our present data provide strong evidence of alterations in G-protein activation mediated by these 5-HT1A receptors in epileptic hippocampus of patients with pharmacoresistant TLE. Alternatively, such changes may represent adaptive mechanisms to compensate for other as yet unknown alterations. Further studies are necessary to elucidate the role of intracellular changes associated with 5-HT1A receptor during the epilepsy process. This study was supported by the National Council for Sciences and Technology of Mexico (grants J110.0130/2009 and 98386).

3.372

THYROID ABNORMALITIES WITH THE USE OF VALPROATE, CARBAMAZEPINE AND PHENYTOIN IN MONO AND POLYTHERAPY AND THEIR CORRELATION WITH BLOOD LEVELS: PROSPECTIVE STUDY AT THE NATIONAL INSTITUTE OF NEUROLOGY AND NEUROSURGERY "MVS" MEXICO

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To determine abnormalities in thyroid function in patients with epilepsy using traditional antiepileptic drugs (AED) in mono or polyteraphy and their correlation with the AED blood levels.

Methods: We prospectively performed serum thyroid stimulating hormone (TSH), thyroxine (T4), triiodothryronine (T3), free thyroxine (fT4) and free triiodothryronine (fT3) and AED levels in 89 patients with epilepsy attending the Epilepsy Clinic at the National Institute of Neurology and Neurosurgery, Mexico city, patients were taking valproate (VPA), carbamazepine (CBZ) or phenytoin (PHT) in mono or polytherapy. Results were analyzed using student t test for parametric variables and Mann-Whitney U-test and Spearman correlation for nonparametric variables.

Results: TSH was elevated in patients taking valproate in mono (p =0.03) or polytherapy (p=0.010). VPA monotherapy increases fT4 (p= 0.023) while VPA polytherapy increases T4 (p=0.037). Carbamazepine in monotherapy and polytherapy reduced fT4 (p= 0.003 & p = 0.009 respectively). Phenytoin monotherapy decreased T4 (p=0.05) and PHT polytherapy increases fT4 (p = 0.009). There was a positive correlation between VPA blood levels and increase of TSH and fT4 levels (p 0.01). We did not find a correlation between the time taking AED and the presence of thyroid abnormalities.

Conclusions: Our study shows that the use of traditional AED in mono or polytherapy produces significant thyroid abnormalities. The use of VPA associates with an increase of TSH and fT4 that also correlates with VPA blood levels. It is important to identify these cases, evaluate them for treatment and eventually determine the clinical relevance of thyroid abnormalities in patients taking AED.

Supported by CONACYT Project: 118715

3.373

CALLOSOTOMY AS AN ADJUVANT TREATMENT IN A PATIENT WITH CRYPTOGENIC CATASTROPHIC EPILEPTIC ENCEPHALOPATHY: CASE REPORT

Dr. René Domínguez, Dra. Clotilde García, Dr. Fernando Soto, Dr. Ramsés Ortiz, Dr. Bernardo García, Dr. Nicolás Téyes, Dr. Carlos Paz. *(Neurology and Neurosurgery Department of PEMEX-Central South High Specialty Hospital)*

BACKGROUND: There has been described only a few cases of untractable epileptic status with multifocal crisis of unknown etiology. Nearly 20 to 30% of epileptic patients are resistant to conventional antiepileptic drugs. Those patients are elictible to receive alternative therapies such as callosotomy to achieve epileptic control, reduce antiepileptic drugs consumption, hence limiting side effects, and improving patient´s life quality.

OBJECTIVE: To present a case report of a patient with cryptogenic catastrophic epileptic encephalopathy (CCEE) who was candidate to receive epileptic surgical treatment as an adjuvant therapy.

CASE REPORT: 6 years old male patient with a non-pathologic perinatal history, normal psychomotor development, who suddenly develops: fever, headache, asthenia, adynamia, sore throat and vomit. At the time of admission he had neurological deterioration characterized by somnolence and generalized tonic-clonic seizures. He was initially managed with *PHT* impregnation, but due to a lack of response he was induced to a barbituric coma with thiopental. His clinical evolution was inadequate because a persistent epileptic status. Many antiepileptic drugs were administered, such as: *PB, Midazolam, VPA, VGB, Dexamethasone, LTG, CZP, ACTH, Propofol, LEV and TPM.* Regardless of multidrug treatment, he continued with poor control of seizures and develops CCEE. EEG shows generalized spike-waves complexes, highvoltage slow waves, polyspike discharges paroxysms. Also he had several drug side effects. That's why he was selected to undergone surgical treatment and callosotomy was performed. Initially he presented clinical and electroencephalographic improvement. Nevertheless 72 hrs after surgery he develop partial motor seizures (almost 135 per day) coreoathetosic movements, multiple organ failure and finally he dies. The frontal cerebral cortex biopsy reports simple neuronal atrophy and serious extensive hypoxic changes with microglial activation.

CONCLUSIONS: Epileptic status has an elevated morbi-mortality on pediatric patients. The secondary development of CCEE entails a lack of response to pharmacological l treatment. Callosotomy is an acceptable adjuvant treatment for this kind of patients. Regardless the employed therapy, CCEE has an elevated sequelae and mortality rates.

3.374

EPILEPSY AND MIGRAINE

Plascencia-Alvarez Noel MD, González-Gómez René I. MD, Juárez-Martínez Erika MD, Maldonado-Torres Gilberto MD, Arrazola-Cortez Edgar MD, Núñez-Orozco Lilia MD Objective: The comorbidity of epilepsy and migraine is common. The purpose of this study was to evaluate this association in a sample of our patient population.

Methodology: This is an observational, transversal study made in "Centro Medico Nacional 20 de Noviembre" from November 2009 to May 2010, in 60 patients over 18 years (27 women and 33 men) with epilepsy according to the ILAE´s criteria.

Results: 37/60 (61%) reported headache. Of these 37 patients, 26% regarded the seizures as a trigger of headache, 59% presented headache from 24 to 72 hours before the seizures, 24% with a diagnosis of migraine after the diagnosis of epilepsy Symptoms preceding the headache: 29% none, 24% Déjà vu, 21% visual disturbances, 12% dizziness. Accompanying symptoms: 24% sonophobia, 20% photophobia, 18% nausea, 10% cacosmia. Triggers for seizures: headache in 26%, stress in 38%. 76% had headache in the first 24 hours after seizures.

Conclusions: One third of patients reported headache of any kind. Of those who reported headache, 27% had migraine´s criteria (prevalence in the general population in México is 12%). The rest presented seizures associated with headache (76%), although only 26% considered that headache triggered their seizures.

3.375

CLINICAL UTILITY OF SHORT-TERM VIDEOELECTROENCEPHALOGRAM MONITORING IN EPILEPSY

González Orizaga Iris Maurilia, Berenguer Sánchez Mauricio , Gutiérrez Manjarrez Francisco, Soto Cabrera Elizabeth, Zavala Ferrer Federico, Campos Villarreal Omar, Alonso Vanegas Mario, Sentíes Madrid Horacio, Estañol Bruno, García Ramos Guillermo. (Department of Neurology and Psychiatry, Laboratory of Clinical Neurophysiology)

Introduction: The Videoelectroencephalogram (VEEG) is the synchronous and simultaneous recording of electrical brain activity and behavior of the patient during a paroxysmal event, which is useful in epilepsy and the differential diagnosis.

Objective: To evaluate the usefulness of VEEG of short duration in epilepsy. Patients and Methods: Retrospective and descriptive. We analyzed 54 studies of VEEG, March 2009 to June 2010, made with digital VEEG GRASS system, using 22 channels for recording EEG, two for eye movements and one for EKG, placed according to the System 10/20 International.

Results: Of the 54 patients, 37 (68.5%) were female and 17 (31.5%) males with a mean age of 33.7 ± 6.2 (range 6-76 years). The study duration was 4.15 hours ± 0.25 (range 1-8 hours). The shipment was diagnosed epilepsy in 29 patients (53.7%) and non epileptic in 25 (46.3%). The type of crisis in the diagnosis of partial seizures in delivery were 43 patients (79.6%) and generalized seizures in 11 (20.4%).

12 patients (22.2%) had seizures during VEEG, 7 seizures and five were non epileptic. Interictal EEG abnormalities were found in 19 patients (35%), all diagnosed with Epilepsy., Of which 14 (79%) had focal epileptiform activity, diffuse slowing in 3 patients (16%), 1 patient (5%) generalized epileptiform activity. 39 patients (72.2%) were referred by neurologists, 9 patients (16.7%) by Psychiatrists, 3 patients (5.6%) per epileptologist and 4 patients by other doctors. The reason of the register was diagnostic in 48 patients (88.9%), preoperative evaluation in 2 (3.7%) and assess the withdrawal of antiepileptic drugs in 4 (7.4%).

Discussion: The VEEG is useful in the diagnosis of epilepsy and the differential diagnosis. In this study we found 19 patients with interictal EEG abnormalities that allowed to confirm the diagnosis of epilepsy. 12 patients had seizures during the study, and 5 confirmed the diagnosis of pseudoseizures. We believe that the reason for the low percentage of crisis during the search was not the duration of the study, but the low frequency of seizures in a few of our patients.

Conclusion: The percentage of records of crisis depends on the characteristics of patients selected primarily on the frequency of crises and time of registration. In any case, the display of the power crisis and record keeping are of great clinical utility. The high cost of prolonged VEEG and the difficulties of its implementation are a limiting factor in our population, so we consider that the short-term record is also useful.

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EVALUATION OF PATIENTS WITH PROBABLE FIRST EPILEPTIC SEIZURE

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Rationale: Diagnosis of episodes resembling a first epileptic seizure (FES) is not always easy. It is estimated that a misdiagnosis of epilepsy in adults occurs in approximately 25-75% of patients. Establishing an incorrect diagnosis affects health and quality of life of patients. We describe epidemiology, clinical and paraclinical characteristics and identify variables that could help in the correct diagnosis in patients with suspicion of FES.

Methods: We included adult patients with suspicion of FES who were sent to electroencephalographic study (EEG). We describe demographic characteristics, clinical manifestations, EEG, brain image (BI) and final diagnosis. We analyzed the three most common diagnoses to identify variables useful for diagnosis.

Results: We identified 95 patients with EEG and diagnosis of probable FES. Of these, 60% were initially evaluated in an outpatient way, 22% hospitalized, 15% in emergency room, and 3% in IUC. 65% were women, mean age 47.5 ± 18 years. 9% had a family history of epilepsy, febrile seizures in 5%, head trauma in 14%, alcohol in 12%, syncope in 6%, diabetes mellitus in 21%, cardiovascular diseases in 24%, renal failure in 8%, stroke in 10%, AIDS and cancer in 6%. 56% had partial seizures and 44% generalized seizures. Clinical manifestations were motor activity in 47%, loss of alertness in 24%, fainted in 4%, psychiatric symptoms in 12 %, blurred vision in 9%, sensory symptoms in 6%, dizziness and anxiety in 1%. Neurological examination was normal in 70%. BI was performed in 85%, 60% were abnormal with focal lesion in 61%, diffuse lesion in 6%, and unspecified lesion in 33%. EEG was abnormal in 35%, 33% had diffuse slowing, focal epileptiform activity in 30%, focal slowing in 27%, and nonspecific activity in 9%. Epilepsy was diagnosed in 26%, 24% had non-epileptic seizures, syncope in 21%, undetermined cause in 11%, movement disorder and migraine in 8%, stroke in 5%, and sleep disorder in 3%. Statistical significance for diagnosis of syncope was reached for blurred vision; BI with focal lesion, and EEG with focal epileptiform activity were important for epilepsy; a clinical episode with duration >5 min was for non-epileptic seizures ($p < 0.05$). See table.

Conclusion: In probable FES there is a heterogeneous range of differential diagnoses. We found, as the main diagnosis: epilepsy and non-epileptic seizures, similar to described in literature. In >50% BI were abnormal, being the most common finding: focal lesion. The

abnormal findings in EEG were generalized slowing and focal epileptiform activity. Variables important to guide the diagnosis were blurred vision for syncope, abnormal EEG and BI for epilepsy, and duration of episode for non-epileptic seizure. In the suspicion of FES the assessment should be based on appropriate clinical history, physical examination and paraclinical data to avoid misdiagnosis.

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CLINICAL CHARACTERISTICS OF SEIZURES IN PATIENTS WITH STURGE-WEBER SYNDROME. IMPLICATIONS ON EVOLUTION

University of Texas Health Science Center at San Antonio (UTHSCSA) and the American Epilepsy Society

Introduction:
In Sturge Weber syndrome, epilepsy is a common feature. Seizures occur in 75-90% of cases that constitute the most disabling neurological symptoms. In the world literature reported age of onset varies from 2 months to 14 years, being more frequent before the year of age. The leptomenigeal angyomatoses is more frequent in the occipital region therefore the seizures more frequently are partial motor features limited to a body part or limb. Have also been observed apparently generalized seizures and infantile spasms typically may precede other seizures. One of the features in this syndrome is the experience in long-term crisis or unilateral epileptic status. The development is not favorable in the presence of epilepsy and intellectual and neurological function. Some points of poor prognosis indicate that early seizures are prone to generalization, increased frequency, increased time post-ictal state, progressive and rapid deterioration and evidence of cerebral atrophy in the area of injury. Prevention of recurrent seizures may diminish the effects of hypometabolism and hypoxia; therefore, the goal is complete seizure control. Management principles for recurrent seizures associated with other conditions also apply to seizure prophylaxis in SWS. Children are initially placed on carbamazepine, with phenobarbital and phenytoin as second-line therapies. If control is not achieved, valproate or topiramate may be added to carbamazepine, with the ultimate goal of monotherapy seizure control with valproate or topiramate. Children who receive no relief from frequent, debilitating seizures are candidates for epilepsy surgery.

Objective: To describe the characteristics of patients with epilepsy of Sturge Weber syndrome and its implications on the evolution in the Hospital Infantil de Mexico in the last 10 years.

Method: The study design is descriptive and Transversal. We performed a review of records of patients with Sturge Weber syndrome and epilepsy in the past 10 years, evaluating the clinical characteristics of seizures and age at onset of the same, given the management and history of Pharmacotherapy .

Results: We evaluated a total of 13 patients in the last 10 years. 61.5 are female and 38.5% male. The onset of the crisis with a mean age of 16.4 months, with the smallest one month and the older is 4 years. The seizure types were observed with partial onset seizures and secondarily generalized increased tone with 41.5%. 11.7% simple partial seizures, complex partial seizures 11.7%, 11.7% Tonic seizures, Infantile spasms 5.8%, atypical absence 5.8%, simple partial with motor symptoms hemicorporeal 5.8% and complex febrile seizures 5.8%. Control of epilepsy is considered when managing to have a six or more months free period of seizures. 61.5% were with proper management, and 38.4% of patients did not. The facial nerve branch V1 mostly affected was 46.1%, V2; 34.6%, V3 19.2%, 76.9% unilaterally and bilateral 23.07%. Per patient affected 38.4% of the three branches, two branches 30.7% and only one branch 30.7%. Cerebral lobe affected: Occipital 16%, Temporal 28%, Parietal 24%, Frontal 32%. The drugs used in the study group were 11 in total, in various combinations, the most used is VPA, more than a half of de cases with 54.5%, followed by the PB with 27.2%, CLB 27.2%, TPM 18.1%, OXC 18.1%, LTG 9.0%, GBP 9.0%, PHT 9.0%, CBZ 9.0%, PRM 9.0%, VGB 9.0%.

Conclusion:
In our study the objective was to compare the world's population with that of our institution, with respect to seizures, the age range we mentioned literature is very variable range, we observed that the age at presentation was smaller this is reflected in the outcome, showing all the patients with important developmental disorders and refractory Epilepsy. Something very important is that in several studies mentioned that the brain most affected lobe is the occipital, in our study was observed more frequently affected temporal and parietal lobe, including total hemispheric conditions, and presence of facial nevus in the three branches and some patients with bilateral involvement, this being reflected in the clinical characteristics of the crisis. The literature emphasizes that crises are more frequent Partial and West syndrome, we found a very important difference: in most widespread are the property of which some had partial onset, and only one patient manifested with epileptic encephalopathy. Most were women. A large number of our patients did not have adequate control.

3.378

ASSESSMENT OF OLFACTORY CAPABILITY OF MESIAL TEMPORAL LOBE EPILEPSY (MTLE) PATIENTS

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Research work on olfactory capability (birhinal) has shown recognition, threshold and memory (Carrol et al, 1993) alterations in MTLE patients. Nevertheless, there are no reports on unirhinal studies in Mexican population.

Objective: Study on the unirhinal and birhinal olfactory capabilities applying standard olfactory tests in our laboratory on recognition, discrimination, threshold and memory of healthy adults and patients with MTLE diagnosis. We evaluated 15 patients (7 women and 8 men) in pair-wise comparisons to a control group (60 women and 40 men) of the same age, educational background and minimental test results.

Results: The results showed significant differences in the identification and recognition tests. We used four odors: rose, orange, cinnamon and lime. MTLE patients showed a decrease ($p<0.05$, Ç2 test) using the left, then the right and then both nostrils for the rose odor. However, the cinnamon, orange and lime odors were identified in a lesser proportion when using the left nostril ($p<0.05$). As discriminating difficulty was raised (nard/jasmine similar scents) the patients showed a lower discriminating capability regardless of the evaluating method (unirhinal/birhinal) in comparison to the control group ($P<0.05$, Ç2 test). When the olfactory threshold was evaluated using the coffee odor, we found that the left nostril showed a higher threshold when compared to the right nostril in TLE patients. When we evaluated using both nostrils, the differences in the concentrations were significantly higher in the patients (2.98X10-5) than in the control group (8.2X10-6).In the olfactory memory analysis we observed that the control group memorized an unfamiliar odor for two weeks; whereas the TLE patients for three weeks. The decrease in the olfactory capability when using the

left nostril may suggest impairment of the left lobe which would show why they cannot label an odor or that the impairment of the right lobe makes them identify an odor as an isolated known entity;In the discrimination tests, patients showed a lesser olfactory capability when using the left nostril. Carroll & Richardson (1993) found that the right TLE patients lose their olfactory short-term which may explain the patients´ difficulty to remember an unfamiliar odor such as that of nards. These findings might be caused by the impairment of the structures related with olfactory functions such as the piriform cortex, hippocampus and entorinal cortex due to TLE.

Conclusion: These results showed that there is an olfactory dysfunction in TLE patients. Further studies are currently being performed to evaluate the diagnostic value regarding localization, lateralization and prognosis of MTL seizures. This project was supported by IN200110 DGAPA grant.

3.379

VOLTAGE-DEPENDANT VERBAL MEMORY. EFFECTS ON THE COGNITIVE FUNCTION THROUGH CHANGING VOLTAGE PARAMETERS IN DEEP BRAIN STIMULATION

Avril Nuche-Bricaire, 3 Marysol Montes De Oca, 2 José Marcos Ortega3, 1,3 David Trejo, 3José María Núñez, 3 Daruny Vazquez, 3Ana Luisa Velasco-Monroy. **(**1Behavioural Neurosciences PhD Program, Facultad de Psicología, UNAM, 2 Neurolinguistics Department and 3 Epilepsy Clinic at General Hospital of México.)

RATIONALE: The left hippocampus is involved with learning acquisition, and verbal short term memory (1). Left mesial temporal lobe epilepsy patients can present naming problems, verbal memory deficit and even acoustic-amnesic aphasia. This language disorder is characterized by memory retention of auditory-verbal traces deficit with inability to repeat 4 item word lists or large sentences, and morphological paraphasias (2). Deep brain stimulation of the hippocampus reduces seizures without impairing memory (3). Nevertheless, neither language nor cognitive function with voltage parameters changes has been studied.

OBJECTIVE: Assess and measure naming and verbal memory before and after increasing of voltage parameters on temporal mesial lobe epilepsy patients with left hippocampal deep brain stimulation.

METHODOLOGY: 4 patients with left hippocampal deep brain stimulation were included. Age 20-27; 3 M, 1F. Initial parameters: 3.5V, 450 msec pulsewidth, frequency 130 Hz, cyclic mode 1 min ON/4 min OFF. We did a clinic neuro-linguistic assessment in order to test fluency, comprehension, repetition and naming. In addition, we include two verbal memory tasks: word list and large sentences repetition as well a 100 picture naming test -50 Snoodgrass & Vanderwart (4) nouns & 50 IPNP (5) action verbs-. After the initial assessment we modified the amplitude parameters from 3.5V to 4.0V. After a 2 hours interval we did the post-test with the same methodology but different items, in order to avoid apathy and tiredness.

RESULTS: No patient showed any significant deficit in language function at the pre condition (3.5V). With the voltage parameter increased to 4.0 V, 3 patients showed a non- significant increased in naming errors. One patient showed a 10% deficit in the picture naming test, compared to pre-condition and had 9 morphological paraphasias. As well, he could not repeat large sentences and needed some repetitions in comprehension assessment. In summary, diagnosis of one patient language deficit turns from mild disnomia (3.5V) in to an acousticamnesic aphasia (4.0V). The deficit was totally reversed when the voltage parameters were decreased. The patients who did not have any specific change on language function showed characteristic symptoms from parahippocampal stimulation so we can say that electrodes precise localization is crucial and these symptoms are very sensitive to small changes in voltage amplitude.

CONCLUSIONS: Deep brain hippocampal stimulation is a good neurosurgical alternative for refractory epilepsy patients. However, fine changes in voltage amplitude could affect specific cognitive functions to go unnoticed in routine neurological assessment. This could affect the patient's life quality. On the other hand, this experiment contributes to study of the hippocampus key roll in language function.

3.380

LANGUAGE LATERALITY IN PATIENTS WITH EPILEPSY AND HEALTHY SUBJECTS BY A DICHOTIC LISTENING TASK

Nuche. Clínica de Epilepsia de Difícil Control. Hospital General de México. Laboratorios Clínicos Azteca. INCMNSZ D. Trejo-Martínez, A. L. Velasco, F. Velasco, J. M. Nuñez, R. Conde, Eloisa Colin-Ramírez, A.

RATIONALE: The aim of this study was to determine if there is advantage in right ear in the perception of words in two groups of healthy subjects (left-handed and right-handed) and one group of epileptic patients by a Dichotic Listening Task.

METHODS: We used 30 pairs of words in which controlled the simultaneous presentation, duration and end of each pair of stimuli, which were presented twice to each subject, constituting a total of 60 pairs for each participant. We included 80 healthy subjects (50 left-handed and 30 right-handed according to a scale of manual preference) and 30 epileptic patients. The Laterality Index (LI) was obtained with the amount of words perceived in each ear as follows: (L-R) / (L+R)=LI. Strong left lateralization (+0.50 to +1), Weak left lateralization (+0.24 to +0.49), Bilateral representation (+0.25 to -0.25), Weak right lateralization (-0.24 to -0.49) and Strong right lateralization (-0.50 to -1).

RESULTS: The results show that in contrast to the left-handed group, right handed subjects have a significant difference (<0.0001) in the perception of words between the right and left ear. Also, there is a clear difference in the frequency distribution of laterality of language among both groups. The group of epileptic patients has a right ear advantage too, but different distribution. CONCLUSIONS: It is possible to observe differences in brain organization of language between patients with epilepsy and healthy subjects using a dichotic listening task, which represents an available option for determining hemispheric dominance for countries in development.

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SURGICAL TREATMENT OF DRUG RESISTANT MESIAL TEMPORAL LOBE EPILEPSY WITH BILATERAL FOCI

Vázquez D, Velasco AL, Velasco F, Núñez JM (Epilepsy Surgery Clinic, Department of Functional Neurosurgery, Stereotaxy and Radiosurgery, General Hospital of Mexico, Mexico City)

Rationale. It is well known that bilateral temporal lobectomy causes severe amnesia; on the other hand, Vagus Nerve Stimulation does not offer important seizure control1 (Engel class IV)2. As a result of this, patients who have drug resistant mesial temporal lobe epilepsy with bilateral foci usually are not offered surgery. Hippocampal stimulation

has proved to be a safe and efficient procedure for patients who are not suitable candidates for temporal lobectomy, specially in those without hippocampal sclerosis3,4,5.

Methods. We present a retrospective review of patients who underwent surgery for treatment of temporal lobe epilepsy. Five of them had bilateral foci. All patients went through a presurgical evaluation process that comprised clinical evaluation, surface EEG, neuropsychological evaluation, MRI, and depth electrode continuous video EEG. Electrodes were placed through occipital burr-holes. The first two patients had a first surgical procedure for electrode implantation and a second surgical procedure for implantation of extension and pulse generator. For the rest of the patients implantation was made in a single surgical procedure.

Results. From June 1999 to July 2008 five patients with mesial temporal lobe epilepsy with bilateral foci have been surgically treated at our Epilepsy Surgery Clinic. The first four patients underwent bilateral hippocampal stimulation; one of them, patient 2, had left hippocampal sclerosis. Patient 5 had right hippocampal sclerosis, she underwent right temporal lobectomy and left hippocampal stimulation. By 18 months follow-up all patients had seizure reduction, with patient 2 in Engel class II and the rest of patients, in Engel class I.

Conclusions. Patients with drug resistant mesial temporal lobe epilepsy who have bilateral foci can be offered surgical treatment. Hippocampal stimulation techniques and its combination with conventional ablative procedures have accomplished seizure reduction with no cognitive sequelae.

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CORTICAL DYSPLASIA IN PATIENTS WITH TEMPORAL LOBE EPILEPSY; MORPHOLOGICAL STUDY OF 60 CASES

Juanita Villeda, M. Alonso, L. Rocha and S. Orozco

RATIONALE: In the present study we characterized neocortical malformations in cases of refractory temporal lobe epilepsy and cortical dysplasia (CD)

METHODS: We studied 60 cases (40 males and 20 females), mean age 34.6 years, of refractory temporal lobe epilepsy and CD, only 8 with preoperative MR imaging suggestive of CD. All patients were studied according to standardized presurgical protocol and submitted to temporal lobectomy and amigalohippocampectomy. The expression and distribution of GFAP, nestin and vimentin, was studied immunocitochemically in T1, T2, and T3 regions.

RESULTS: We found marked dislamination in all areas of the cortex, neuronal loss, amylaceous bodies, neuronal cytomegaly with cytoskeletal disorganization containing dense fibrillar cytoplasmic aggregates, dysplastic neurons, balloon cells with atypical nuclei, often with binucleation, and abundant glassy eosinophilic cytoplasm. CD was classified as Type IA in 8.3%, Type IIA in 50%, and Type IIB in 15% of cases. Combined Type IA and IIA were found in 5%, Type IIA and IIB in 16.6% and Type IA and IIB in 1.6% of cases. GFAP, nestin and vimentin were highly expressed in the majority of neurons in the cortical areas as well as the hippocampus.The majority of balloon cells were found in the white substance. Expression of nestin was increased only in balloon cells and dysplastic neurons.

CONCLUSIONS: These findings suggest that malformations of cortical development, up regulation of the astrocytic response as an astroglial dysfunction, and possible alterations in the blood brain barrier contribute to high epileptogenic activity in these patients.

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HOT WATER EPILEPSY: CASE REPORT

Sandoval-Pacheco R. MD1, Avalos-Plata R. MD1, Herrera-Mora P. MD2, Ruiz-García M. MD2, García-Briseño A. MD3, Pediatric Neurology Resident 1, Neurology Department2, Neurophysiology Department3, Instituto Nacional de Pediatría. SSA. México.

INTRODUCCION
The Term “reflex epilepsy” describes a seizure precipitated by an external sensory stimulus. The role of stimuli in provoking seizures has been known since 1850s; several types of seizures have been described since then (1). In approximately 5% of epilepsy patients, seizures triggered off by a specific sensory stimulus (2). Certain epileptic seizures are regularly precipitated by specific stimuli. Most of these stimuli are sensory in nature, but some are represented by complex activities involving several different sensory systems or higher brain functions (for example listening music or reading epilepsy). Intermittent light is by far the most common sensory precipitant of seizures (3). Hot water epilepsy is a rare disorder in our medium; this is precipitated by the stimulus of bathing with hot water.

PURPOSE:
Our aim is to outline the clinical and video-electroencefalographic (V-EEG) features of one patient with hot water epilepsy (HWE), a rare and unique form of reflex epilepsy.

PATIENT AND METHOD:
Male 7 months old, presented paleness, hypotonia and loss of consciousness at the hot water immersion per 15 seconds and somnolence during two hours. The patient was examined in cardiac, neurologic and biochemical aspects. Electrocardiogram, Magnetic Resonance Imaging (MRI) laboratory test and the clinical exam were normal. Interictal electroencephalogram (EEG) recording was normal too. Video-EEG was performed during the immersion in hot water at 35°C, repeating the event described with clinic and electroencephalographic correlation. The patient was managed with valproic acid for three months and avoided the immersion in hot water; he is free of seizures without treatment since 25 months ago with normal neurodevelopment.

DISCUSSION:
The underlying mechanisms of HWE remain unclear; some may have a genetic basis with added environmental influence. In HWE the interictal EEG is usually normal, but 15-

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LANGUAGE LATERALITY IN PATIENTS WITH EPILEPSY AND HEALTHY SUBJECTS BY A DICHOTIC LISTENING TASK

D. Trejo-Martínez, A. L. Velasco, F. Velasco, J. M. Nuñez, R. Conde, Eloisa Colin-Ramírez, A. Nuche. Clínica de Epilepsia de Difícil Control. Hospital General de México. Laboratorios Clínicos Azteca. INCMNSZ

Content:

RATIONALE:
The aim of this study was to determine if there is advantage in right ear in the perception of words in two groups of healthy subjects (left-

handed and right-handed) and one group of epileptic patients by a Dichotic Listening Task.

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CONCLUSIONS:
It is possible to observe differences in brain organization of language between patients with epilepsy and healthy subjects using a dichotic listening task, which represents an available option for determining hemispheric dominance for countries in development.

3.385

SURGICAL TREATMENT OF DRUG RESISTANT MESIAL TEMPORAL LOBE EPILEPSY WITH BILATERAL FOCI

Vázquez D, Velasco AL, Velasco F, Núñez JM Epilepsy Surgery Clinic, Department of Functional Neurosurgery, Stereotaxy and Radiosurgery, General Hospital of Mexico, Mexico City

Rationale. It is well known that bilateral temporal lobectomy causes severe amnesia; on the other hand, vagus nerve stimulation does not offer important seizure control1 (Engel class IV)2. As a result of this, patients who have drug resistant mesial temporal lobe epilepsy with bilateral foci usually are not offered surgery. Hippocampal stimulation has proved to be a safe and efficient procedure for patients who are not suitable candidates for temporal lobectomy, specially in those without hippocampal sclerosis3,4,5.

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3.386

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Conclusions:
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Poster Session 2
8:00 a.m.-6:00 p.m.

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PREDICTORS OF FIVE-YEAR REMISSION IN FOCAL EPILEPSY OF UNKNOWN CAUSE

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Rationale: Focal epilepsy of unknown cause (FEUC) is a heterogeneous clinical disorder including patients with severe refractory forms and patients with a fairly good prognosis. Predictors of prognosis in FEUC are poorly understood. Methods: Two thousand and eightythree patients with FEUC were consecutively seen from April 1987 to April 2010 in two Epilepsy Centers located in Reggio Calabria and Catanzaro, Calabria, Southern Italy. 909 patients were excluded because of insufficient anamnestic data, psychogenic seizures, major psychiatric disorders, isolated seizures, absence of neuroimaging study or presence of brain lesions except for scattered T2-hyperintense spots on hemispheric white matter. The following variables were considered : age, gender, age at onset of epilepsy, family history of epilepsy or febrile seizures (FS), perinatal factors, personal history of FS, personal history of status epilepticus, type of seizures, presumed lobar localization (frontal, temporal, parietal, occipital, undetermined), interictal EEG (normal, abnormal, unilateral, abnormal bilateral), type of recruitment (incident or prevalent case). Survival curves were generated according to the Kaplan–Meier method and compared with the log-rank test. The end point was the cumulative time-dependent chance of 5-yrs remission after treatment start. Independent predictors of remission were tested by multivariate analysis using Cox proportional hazards function models. Results: The sample included 1174 patients (610 women and 564 men) aged 1 to 98 years who were followed for 1019.4 person-years. 105 cases presented 5-yr remission during follow-up. Of these, 36 were never treated. The cumulative probability of remission was 9% at 5 years, and 14, 18, and 21% at 10, 20, and 30 years. At univariate analysis, factors predicting remission included female gender, older age at onset, family history of epilepsy, drop attacks, and presumed lobar localization (fig. 1-2). Independent predictors of remission were older age at onset (Hazard Ratio, HR for each increasing year 1.001; 95% confidence interval, CI 1.000- 1.002), family history of epilepsy (HR 1.6; 95% 1.1-2.4), seizures with loss of consciousness (HR 1.7; 95% CI 1.1-2.6), secondarily generalized seizures (HR 1.6; 95% CI 1.0-2.5), dropattacks (HR 0.2; 95% CI 0.0-0.8), parietal epilepsy (HR 3.2; 95% CI 1.4-7.1), occipital epilepsy (HR 1.8; 95% CI 1.1-3.2), and being an incident case (HR 2.9; 95% CI 1.8-4.6). When limiting the analysis to incident cases, independent prognostic predictors were only loss of consciousness and occipital epilepsy. Conclusions: Up to one fifth of cases with FEUC attain 5-yr seizure remission during follow-up. Older age at onset, family history of epilepsy, seizure type, and lobar localization are independent prognostic predictors. However, only lobar localization and seizures accompanied by loss of consciousness are favorable prognostic predictors in patients seen at diagnosis.

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SCN1A-TARGETED SIRNA IN RATS CAUSES BEHAVIORAL IMPAIRMENT: IMPLICATIONS FOR DRAVET SYNDROME

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Rationale: Dravet syndrome (DS) is an epileptic disorder that affects infants during the first year of age and has devastating consequences on the patient's cognitive development. This disorder has been associated with autosomal dominant mutations of the SCN1a gene, coding for a voltage gated sodium channel, Nav 1.1, that is mainly localized in GABAergic interneurons and not pyramidal cells. It is widely believed that the presence of seizures during development is the main cause of cognitive impairment in this syndrome. However, because interneurons play a critical role in driving neuronal processing, it appears likely that SCN1a mutations result in abnormal information processing, independently of seizures.Methods: To control the onset of SCN1A deficit and begin to elucidate its contribution to cognition and behavior, we used a siRNA-mediated RNA interference approach to knock down expression of SCN1A. Nine adult (P60-P90) Sprague-Dawley rats were implanted with an injection cannula into the left lateral ventricle and a custom EEG recording electrode into the right dorsal hippocampus CA1 region. Rats were injected with siRNA complexes once daily for 4 days (4 control, 5 SCN1A). Each day rats were placed in a circular arena with 3 objects at the perimeter, and EEG and position data were recorded during 10 minute sessions. On the last day, rats were assessed for performance in an object recognition task. The rat was habituated to the 3 objects in the arena for 10 minutes. In the first test for spatial memory, one object was moved to a new location, and the rat was allowed to explore this novel spatial configuration for 10 minutes. In the second test for novel object recognition, one object was replaced with a new object, and the rat was allowed to explore for an additional 10 minutes. The percent time spent near each object was measured. Results: SCN1A-targeted siRNA treatment in rat neuroblastoma cells resulted in a mean 61% ($t(2)=-8.008$, $p=0.0152$) suppression of SCN1A expression after 24 hours (Figure 1A). After four days of intraventricular administration of siRNA complexes, rats treated with SCN1A-targeted siRNA were impaired on a spatial task of object recognition. While rats that were delivered control siRNA spent more time exploring the moved object ($F=9.03$, $p=0.0155$), the SCN1A group showed no preference ($F=2.19$, $p=0.155$; Figure 1C). The SCN1A group showed no significant impairment on novel object recognition, but there was a trend for a weaker preference to the novel object compared to the control group (Figure 1C). In support of this difference in a task of spatial memory, we found a trend toward reduced theta power in the dorsal hippocampus (Figure 1B). Seizure activity was not observed during any recordings.Conclusions: These results suggest that SCN1A-targeted siRNA treatment in vivo is sufficient to cause spatial cognitive impairments, independently of seizures. In consequence, it could be argued that seizures may not be the only contributors for the cognitive impairments in this syndrome. This work was supported by NIH Grants RO1NS056170, RO1NS041595 and R21MH086833-01A2.

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ASSOCIATION BETWEEN INFANTILE SPASMS AND THE "SHAKEN-BABY SYNDROME"

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Rationale: Infantile spasms (IS) is a severe epileptic encephalopathy of infancy with a poor developmental outcome. The pathophysiologic process underlying IS is still not understood. They are characterized by a great diversity of many etiologies both acquired and genetic that all manifest with the same clinical presentation. Animal models that have been developed are not able to reproduce every aspect of IS. Therefore, studying the possible etiologic relationship between known acquired brain injuries and IS in human beings could provide new insights into the understanding and eventually the prevention of this disorder.Methods: We describe two cases of infantile spasms that developed several weeks after the infants had suffered from a non accidental head injury (NAHI) or "shaken-baby syndrome".Results: Two previously normal male infants suffered from NAHI at the age of (1) one and (2) three months. During the acute stage, both of them developed multifocal seizures that were controlled with Phenobarbital and Phenytoin. Neuroimaging studies showed multiple subdural hematomas, areas of parenchymal contusions, subarachnoid and/or intraventricular hemorrhages and, subsequently, (1) encephaloclastic lesions or (2) diffuse brain atrophy. In patient No 1, Phenobarbital was continued till the age of four months and then, although the infant was seizure free, replaced with Clobazam as the EEG records were still capturing multifocal epileptic discharges. Patient No 2 continued on Phenobarbital for one month and had no recurrence of seizures upon tapering. Both infants developed IS at the age of (1) five and (2) six months. EEG records were characterized by typical hypsarrhythmia. In both cases, spasms were rapidly controlled with Vigabatrin. Both children were seizure free at (1) fourteen months and (2) five-years follow-up but were significantly developmentally delayed.Conclusions: Our two patients highlight the risk of young children suffering from NAHI to develop infantile spasms. These children seem to respond well to Vigabatrin as first line therapy. A better knowledge of the incidence of IS following NAHI could help us better understand the link between NAHI and IS as well as develop neuroprotective treatments to prevent the occurrence of this severe form of epilepsy.

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EPILEPSY CO-MORBIDITY IN COMPLEX CHILDHOOD DEVELOPMENTAL DISORDERS: SEIZURE SUSCEPTIBILITY IN A GENETIC MOUSE MODEL OF RTT SYNDROME DEMONSTRATES AGE AND GENOTYPE INTERACTIONS

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Rationale: Epilepsy is a common co-morbidity in a number of developmental disorders including autism, is particularly associated with the occurrence of developmental regression, and seizures are often the most disrupting symptom of these disorders for the patient, pediatricians and family. Epilepsy is represented in the great majority of girls heterozygous for mutations in the Xlinked gene MECP2 associated with the developmental disorder Rett Syndrome (RTT). RTT shares many symptoms with autism, and other developmental disorders, including a developmentally complex emergence of symptoms over the lifetime of the individual. These symptoms include a broad developmental regression triggering diagnosis between 12 to 18 months of age; yet seizures typically began 3 to 6 years later and interestingly remit in adulthood. To understand the pathogenesis of epilepsy in RTT and its resolution in adulthood we measured differences in electrically-evoked seizure thresholds between heterozygous MeCP2 knockout mice (MeCP2+/-, female) and wildtype littermates (C57BL/6J background) over adult development.Methods: The electroconvulsive shock threshold (ECT) for generalized and maximal seizures was measured in separate groups of mice starting at 10, 20 and 36 weeks of age and shocks were delivered at constant current via auricular electrodes. ECTs were determined using a ramping procedure in which mice were tested once per day. The starting current was 20 mA and the daily current increment was 2 mA. The ECT for generalized seizure (GECT) was taken as the current level at which mice first displayed loss of posture and bilateral limb clonus. The value at which mice displayed tonic extension of the hind limbs was scored as a maximal seizure (MECT). Results: Results showed significant effects of age (P = 0.006) and genotype (P=0.0005) on GECT as well as a significant interaction between these two parameters (P=0.045, 2-way ANOVA). A significant effect of age was also noted for MECT (P=0.004) with results showing that older mice have a lower threshold; however, there was no effect of genotype. A trend towards an interaction effect on MECT between age and genotype was noted (P=0.07) suggesting that a differential effect of age on wild type compared to knockout mice may also emerge as the study continues. Current results demonstrate differential effects of age on seizure susceptibility in mice genocopying MeCP2-null mutations in RTT. These interactions are primarily driven by a decrease in seizure susceptibility with increasing age when measured by GECT. Conclusions: These mice may reflect the complex development of epilepsy in RTT and our findings may provide insight into other developmental disorders where epileptogenesis occurs in later stages childhood. Furthermore this work provides an important and novel model for understanding interactions between development and genetics in the pathogenesis of epilepsy.

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POTENTIAL NOVEL MOLECULAR PLAYERS IN HOMEOSTATIC PLASTICITY OF HIPPOCAMPAL NEURONS IDENTIFIED BY GENE EXPRESSION PROFILING

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Rationale: It is well known that limbic seizures associated with temporal lobe epilepsy are characterized by aberrant and unpredictable neuronal hyperexcitability. Failure of homeostatic plasticity (a process by which neurons maintain a physiologic balance between neuronal excitation and inhibition) is hypothesized to play a large role in epileptogenesis. However, the molecular basis of this important plasticity has yet to be elucidated. Homeostatic plasticity can be induced in primary dissociated neuronal culture. Prolonged blockade of neuronal activity by treating neurons with Tetrodotoxin (TTX, an inhibitor for voltage-gated sodium channels) leads to a homeostatic increase in synaptic transmission and intrinsic excitability. Conversely, prolonged enhancement of neuronal activity by treating neurons with bicuculline (GABAA receptor antagonist) results in a homeostatic decrease in synaptic transmission and intrinsic excitability. Recently this plasticity was shown to be dependent on transcription, suggesting that regulation of gene expression mediates its induction. Methods: To identify key molecular players of homeostatic plasticity, we performed cDNA microarray analysis on the rat dissociated hippocampal cultured neurons in which global homeostatic plasticity was induced by 48 hr treatment with 0.5 ¼M TTX or 20 ¼M bicuculline or control. Results: Our microarray analysis against rat whole genome Agilent array of 41012 genes revealed 1664 genes whose expression changed significantly upon TTX and bicuculline treatment. We observed over-representation of the genes involved in "synaptic transmission", "transmission of nerve impulses", and "behavior". In particular, overrepresentation of genes involved in "K+ ion transport" caught our

attention since most of them encode K+ ion channels that critically function to dampen neuronal excitability. TTX treatment repressed 11 out of 12 K+ channel genes whereas BC treatment induced 4 out of 7 K+ channel genes. We identified binding sites in these genes for transcription factors such as CREB and JUN. In particular, a significant bidirectional change was found for genes responsible for A-type potassium current, which mediates the duration of time between action potentials and thus serves as a critical brake for repetitive firing of action potentials. In addition to confirming our microarray data with real time PCR and western blotting, we are performing whole-cell patch clamp recording to determine the roles of activity-induced changes in K+ channel expression in homeostatic plasticity of intrinsic excitability. Conclusions: Together, our current findings suggest that activity-dependent expression of ion channels and their associated proteins contribute significantly to the stabilization of hippocampal neuronal excitability by serving as key proteins in the molecular mechanisms governing homeostatic plasticity. These predictions warrant further research, and may provide novel targets for the development of both preventative and therapeutic treatments for epilepsy and other hyperexcitability-associated diseases.

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FLUOXETINE REVERSES BOTH AN ALLOCENTRIC SPATIAL LEARNING DEFICIT AND REDUCED NEUROGENESIS IN A RODENT KAINATE MODEL OF MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Adult hippocampal neurogenesis supports certain forms of spatial learning and memory, and is significantly reduced with aberrant connectivity in Mesial Temporal lobe epilepsy (MTLE), leading to the hypothesis that abnormal neurogenesis may play a causal role in learning and memory impairment in these patients. We used a combination of watermaze testing in both patients and a rodent model of MTLE to investigate this hypothesis. Methods: Using a virtual watermaze, we ascertained the patterns of spatial learning and memory deficits in patients with MRI positive hippocampal sclerosis and compared these to deficits seen using a Morris watermaze in kainate treated adult rats, in whom the level and quality of neurogenesis was also examined. We also treated separate groups of chronically epileptic animals with one month of oral fluoxetine, an SSRI found to increase hippocampal neurogenesis, or vehicle, prior to water maze training. Results: An identical pattern of deficits, consisting of specifically impaired allocentric, but not egocentric, spatial learning was identified in both animal and patient groups. This was associated with quantitatively reduced and qualitatively abnormal hippocampal neurogenesis in the kainate treated animals. Treatment with one month of oral Fluoxetine prior to training restored both hippocampal neurogenesis and allocentric spatial learning to normal in kainate treated rats. Conclusions: These findings suggest that altered neurogenesis may be an underlying mechanism of spatial learning impairment in MTLE and suggest that fluoxetine may have a role in treating learning deficits in these patients.

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THE EFFECT OF EARLY LIFE SEIZURES ON SYNAPTIC PLASTICITY IN THE PREFRONTAL CORTEX LATER IN LIFE

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Rationale: Early life seizures (ELS) are often associated with mental retardation, learning and memory deficits in adulthood and post-neonatal epilepsy. Functional studies of the effects of ELS on the brain later in life often focus on the hippocampus, fewer studies have looked into functional changes in the neocortex. The medial prefrontal cortex (mPFC) is a particularly attractive target for future studies into the effect of ELS on the neocortex. This is because of its strong reciprocal connections to the hippocampus and well-documented role in mediating tasks that require learning, memory and attention, functions that are thought to be involved in cognitive deficits seen in adults and adolescents who have experienced neonatal seizures. PFC synapses, like those in the hippocampus, show a substantial amount of plasticity both long- and short-term. Short-term plasticity (STP) in the PFC is thought to be a molecular correlate of short term working memory, and may have a role in attention. This study examines STP in a layerand frequency- dependent manner in order to determine the long-lasting consequences of ELS on PFC function. Methods: Sprague-Dawley rat pups received a total of 65 flurothyl seizures from postnatal day (P)6 to P17. Extracellular field potentials evoked in LII or LV of the prelimbic region of the mPFC were recorded in LV in ELS (N=3) and littermate controls (N=3) at P27-P36. The frequency dependence of short-term post-tetanic potentiation (PTP) in LII-LV circuits and LV-LV circuits was probed using a baseline single test pulse stimulation delivered repeatedly at 0.1Hz (low baseline) or 0.5Hz (high baseline) and a 50Hz tetanus, 15 pulses, delivered one time. In addition to PTP, paired pulse facilitation was assessed at interpulse intervals varying from 6 ms (150 Hz) to 200 ms (1.7Hz). Stimulus number dependent plasticity was also assessed through examination of the fEPSP during 50 Hz stimulation. Results: In ELS animals, we found a significant increase in PTP in LII-LV circuits under the low baseline stimulation paradigm, alongside a significant decrease in stimulus number dependent plasticity in LV-LV connections ($p<0.01$, two-way repeated measures ANOVA). No change was noted in PTP with high baseline stimulation in LII-LV, or in LII-LV stimulus number dependent plasticity. PTP in LV-LV connections was also unaffected by ELS. It should also be noted that LII-LV facilitation was slightly increased in the ELS group (ns). Conclusions: The PFC is a critically important but vastly understudied brain region in the field of early life epilepsy research. While traditionally research has focused on the hippocampus, recent evidence indicates that alterations in PFC circuitry may also be responsible for some ELS-induced behavioral deficits. The results presented further our understanding of the deleterious neurodevelopmental consequences of ELS on the PFC by showing long-lasting changes in STP. In the future, this knowledge can be used to develop targeted drug therapy to ameliorate some of the cogntive deficits of ELS. This work was supported by NIH Grants RO1NS056170 and RO1NS041595.

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HIPPOCAMPAL THETA RHYTHM AMPLITUDE IS REDUCED AFTER INTRASEPTAL INJECTION OF GAT1-SAP

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Rationale: The medial septum, through theta rhythm generation, inhibits the appearance of interictal spikes and seizures observed in the hippocampus in epileptic animals from the pilocarpine model of Temporal Lobe Epilepsy (TLE). The antiepileptic effect of the theta functional state is probably produced by a common functional mechanism between abnormal synchronization (epileptic spikes) and normal synchronization (theta rhythm) or by increased hippocampal thresholds by septal inputs (for review see Colom & Garrido-Sanabria, 2007). In the pilocarpine model of TLE, Colom et al. (2006) and Garrido-Sanabria et al. (2006) have determined that medial septal (MS/DB) neurons increase their firing rates during chronic epilepsy and that the GABAergic neurons from both MS/DB and lateral septal regions are highly and selectively vulnerable to the epilepsy process. Septal GABAergic neurons exclusively inhibit hippocampal GABAergic

interneurons (Freund and Antal, 1988). Thus, their destruction will disturb the hippocampal theta rhythm by increasing hippocampal inhibition, decoupling pyramidal cells thus promoting desynchronization and facilitating the development of abnormal islands of excitation. Methods: To investigate the exact role of the MS/DB GABAergic neurons in hippocampal theta rhythm generation and its antiepileptic role, the antibody gamma amino butyric acid transporter 1 (GAT1) conjugated to saporin (SAP) was injected (3¼L, 5 ¼L, and 6 ¼L at 325ng/¼L) in the MS/DB of adults Sprague Dawley rats. Subsequently, the effects of the septal GABAergic neuronal loss in hippocampal function were investigated by hippocampal EEG recordings from freely moving rats. Results: At 3 ¼L, 5 ¼L and 6 ¼L injections, Population estimates of MS/DB neurons were analyzed using a stereological approach. A significant reduction (75%-90%; p<0.0001) in the MS/DB GABAergic population was observed. Glutamatergic and Cholinergic MS/DB neurons were only statistically significant at 6¼L. In the freely moving rats, there was an observable decrease in theta amplitude (3 ¼L; 20% and 5 ¼L; 30%), but there was no significant difference in frequency or presence of abnormal activity in the EEG. Conclusions: The destruction of 70-80% of MS/DB GABAergic neurons produce a moderate reduction of theta amplitude (20-30%) and this disinhibition is not enough to induce spontaneous epileptic activity.

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SPLENECTOMY MODULATES EXPERIMENTAL SEIZURES INDUCED BY CHOLINERGIC OR GLUTAMATERGIC ACTIVATION

D. Janigro

Rationale: While a role for the blood-brain barrier (BBB) in seizures has been accepted, only recently an unexpected contribution of circulating immune cells to the development of acute seizures has been demonstrated in animal models. Endothelial-leukocyte interactions have been shown to contribute to pilocarpine-induced epileptogenesis, and anti-inflammatory regimens aimed at reducing adhesion of white blood cells to the vascular wall prevented status epilepticus (SE; Nat.Med. 14, 1377-1383 (2008); Neurobiol.Dis. 33, 171-271 (2009)). In particular, CD8+ natural killer T cells appear to be involved 1 Since the spleen is a chief regulator of leukocyte activation, and in particular CD8+ mobilization, we wished to test the hypothesis that splenectomy prevents pilocarpine-induced SE. Since cholinergic and glutamatergic receptors are expressed on B- and T-cells (J.Immunol. 170, 4362-4372 (2003); J.Neuroimmunol. 194, 83-88 (2008)), kainic acid and pilocarpine were used as SE inducers. Methods: Rats were monitored for EEG and behavioral changes throughout the experiments. Splenectomy was performed either before (>4 hrs.) or after (3 hrs.) exposure to pilocarpine (350 mg/kg) or kainate acid (10 or 15 mg/kg). Immunocytochemical analysis was used to measure CD3+ cells in spleen. Seizures were quantified by joint time frequency analysis.Results: After SE, spleen displayed a great increase of CD3+ cells regardless of the trigger used to induce seizures. Splenectomy prevented seizure development in all pilocarpine-treated rats (n=9 per group). Low dose kainate caused behavioral modifications that were entirely prevented by splenectomy (n=3). At the convulsive dosage, KA seizures were decreased but not entirely abolished in splenectomized rats (n=4). Splenectomy also prevented SE-induced mortality. Conclusions: Our results show for the first time that splenectomy prevents SE (pilocarpine) or decreases seizure burden (KA) in animal models of acute seizures based on chemical activation of glutamatergic or muscarinic receptors. We hypothesize that white blood cell activation by kainate or pilocarpine may be responsible for blood-brain barrier disruption that precedes seizures.

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QUANTITATIVE VIDEO-EEG IN A MOUSE MODEL OF NEONATAL ISCHEMIC-SEIZURES: AGE-DEPENDENT EFFICACY OF PHENOBARBITAL

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Rationale: Ischemia in the immature brain is an important cause of refractory seizures. The exact timing of neonatal stroke onset is usually unclear and the diagnosis delayed until presentation with seizures a few to several hours later. Neonatal electrographic seizures often respond poorly to anticonvulsant drugs with a GABA_A agonist mechanism of action. To investigate the anti-seizure efficacy of the first line anticonvulsant and GABA_A- agonist phenobarbital on neonatal ischemic-seizures, we utilized unilateral carotid-ligation to produce ischemia and acute ischemic-seizures in postnatal day 7, 10 and 12 CD1 mice. Methods: Unilateral ischemia was induced by right carotid permanent-ligation. Acute ischemic post-stroke seizures were recorded using video-EEG in P7, 10 and 12 pups with sub-dermal scalp electrodes. After recording baseline post-stroke video-EEGs each pup received IP injections of 25mg/kg loading doses of sodium phenobarbital. Quantitative video-EEG analysis was done for the same duration of pre- and post-treatment EEGs using Pinnacle (Pinnacle technology Inc., KS) seizure scoring and Insight software (Persyst development corp., AZ). Post-ligation brains were examined for stroke-injury and along with age-matched naïve brains processed for immunohistochemical and western blot analysis evaluating expression profiles of the adult-form electroneutral chloride co-transporter KCC2.Results: Phenobarbital was an efficacious antiseizure agent in P12 stroke-injured pups with robust ischemic seizures. At P12 phenobarbital stopped both the occurrence of behavioral seizures as well as the associated electrographic seizures that were quantified as time spent seizing (n=6) on EEG. Power spectrum analyses in the 0.5-32Hz range were also significantly reduced after treatment in the seizing P12 pups. However, at P7 phenobarbital failed to stop both electrographic and behavioral ischemic seizures (n=10). Post-treatment EEG power spectrums were marginally lowered and associated with lower spike-wave amplitudes on the EEG traces. The duration and counts of seizure events, however, remained unaffected. Partial anticonvulsant efficacy was observed at P10 (n=2) for both time spent seizing and reduction in EEG power. An age-dependent increase in KCC2 expression was established in the maturing CD1 mouse brain from postnatal ages P3 to P22.Conclusions: Anticonvulsant efficacy of phenobarbital for treating acute ischemic-seizures was age-dependent in postnatal pups. Age-dependent increase in the hyperpolarizing effects of the GABA_A agonist may depend on the increasing KCC2 expression profile detected in the maturing CD1 mouse brains. Inefficacious anticonvulsant action at P7 and partial efficacy noted at P10 indicate that ischemia at postnatal ages between P7- P10 may best model neonatal ischemic-seizures in CD1 mice. Establishing this in-vivo model of ischemic-seizures to mimic the clinical condition and response to current first-line treatment protocols will help test novel anti-seizure drugs and therapeutic interventions for evidence-based management of acquired neonatal seizures.

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ACTIVATION OF SUICIDAL IDEATION WITH ADJUNCTIVE RUFINAMIDE IN BIPOLAR DISORDER

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Rationale: Antiepileptic drugs are effective psychotropics, especially for bipolar disorder, which leads to their use off-label in treatment refractory cases. A recent publication suggests that rufinamide may be beneficial adjunctively for bipolar disorder with comorbid psychopathology. This report addresses two negative cases with significant psychiatric adverse effects. Methods: Case analysis with literature reviewResults: Case 1: 38yo female with treatment resistant rapid cycling bipolar disorder had failed rational polypharmacy. Rufinamide (200mg qhs titrated to 400mg total daily dose) was initiated as an adjunctive agent to her regimen of quietapine, olanzapine, verapamil, and lamotrigine. Within one week, the patient reported increased depression with change from passive to active suicidal ideation, and increased irritability. With discontinuation of rufinamide, depressive severity decreased with only passive suicidal ideation, and decreased irritability. Case 2: 33yo female with treatment resistant psychotic bipolar depression, posttraumatic stress disorder, intermittent explosive disorder and generalized anxiety disorder had failed rational polypharmacy and electroconvulsive therapy. Rufinamide 200mg bid was initiated as an adjunctive agent to her regimen of escitalopram, ziprasidone, haloperidol, clonazepam and zolpidem. Within two days, increased agitation was noted; over the ensuing five days, the patient reported both further worsening of agitation and increased suicidal ideation with command auditory hallucinations. Following discontinuation of rufinamide, agitation diminished and suicidal ideation retuned to baseline. Conclusions: Rufinamide may lead to increased suicidal ideation in treatment refractory bipolar patients. Secondary to the course of severe bipolar disorder, rufinamide cannot be specifically implicated; however, clinicians should be aware of this potential significant adverse effect.

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LEVETIRACETAM MONOTHERAPY IN CHILDREN WIH EPILEPSY IN CHUNGBUK, KOREA

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Rationale: Levetiracetam had been used in adjuvanctive Therapy. Levetiracetam is also used in monotherapy in other coutries, so we also studied the Levetiracetam monotherapyMethods: We retrospectively studied the type of epielpsy, EEG, Brain MRI, dose of drug. We studied 101 children who visited our hospital because of seizure since August 2007 to July 2009. Results: The Age is from 1 month to 20 years 1) The mean age of taking Levetiacetam initialy is 11±4 years(from 3 years to 21 years). 2) The types of epilepsy were Partial in 57.4% and generalized in 42.6%. 3) The mean dose started initialy is 6±4mg/kg/day (from 2mg/kg/day to 30mg/kg/day). The mean final dose is 30±8mg/kg/day (from 6mg/kg/day to 60mg/kg/day). 4)The mean duration of therapy is 21±11months, and the duration of therapy ranged from 1 to 38months. 5) 85.1% of patients became seizure free, 88.1% decresed at least 50% reduction in seizure during 12 months. 6) The side effects is that behavioral change is 8, asthenia is 2, cognitive change is 1, rash is 2, headache is 5, inadequate seizure control is 2, increased seizure is 5. 7)Levetiracetam was discontinued because inadequate seizure control is 2, increased seizure is 5 and side effects is 2. Conclusions: We studied efficacy and tolerability of monotherapy of Levetiracetam. Levetiracetam is effective and tolerable in monotherapy of epilepsy.

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INTER-RATER RELIABILITY OF ENGEL AND ILAE SEIZURE OUTCOME CLASSIFICATIONS

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Prevett, M. J. Harris, W. P. Gray

Rationale: Seizure outcome is central to the assessment of overall outcome following epilepsy surgery, vital to adequately informing patients. Outcome is commonly classified based upon modifications of the Engel (Classes I-IV) or International League Against Epilepsy (ILAE; Classes 1-6) systems. There is, however, a lack of data assessing inter-rater reliability for either or any comparison of them. In addition, there are few studies of outcome for resective surgery or vagal nerve stimulation (VNS) in children, with ongoing controversy about whether either are appropriate outcome measures in this age group. Methods: Using Cohen's kappa (k), we evaluated inter-rater reliability of 2 surgical trainees (not involved in decision for or conduct of surgery) for the Engel and ILAE systems when assessing the outcome of all patients with a minimum of 12 months follow-up after undergoing surgery for medically intractable seizures at the Wessex Neurological Centre between 2001 and June 2009.Results: 102 patients fulfilled the inclusion criteria (55 male; 51 children <18 years). Median age at surgery was 24.6 (range 1-62) years with median follow-up 29 (12-92) months. 75 patients underwent resective surgery (51 adults; 24 children): 35 with hippocampal sclerosis, 8 cortical dysplasia, 17 tumours, 5 cavernous haemangioma, 3 dual pathology (hippocampal sclerosis + ganglioglioma, temporal cortex sclerosis or subacute infarct), 1 tuberous sclerosis, 1 arterio-venous malformation; in 5 no histopathological diagnosis was made. 26 underwent VNS implants and 1 disconnection (all children). At last follow-up, Observer 1 (O1) classified 88% (n=67) and Observer 2 (O2) 87% (n=66) of patients as either Engel I or II (free from or rare disabling seizures), while 83% (O1; n=63) and 80% (O2; n=61) respectively were classified as seizure free. 73% (O1; n=56) and 68% (O2; n=52) were classified as ILAE 1 or 1a. The ILAE system had a very good degree of inter-rater reliability (k0.83; 95% confidence intervals, CI, 0.74, 0.91), the highest in our study. The Engel classification system similarly had good inter-rater reliability (k0.76; 95%CI 0.66, 0.85). For pediatric resective cases, the inter-rater reliability was very good for both classifications: ILAE k0.88; 95%CI 0.68, 1 and Engel k0.82; 95%CI 0.63, 1. When assessing VNS implantation outcome, the inter-rater reliability was moderate for both classifications: ILAE (k0.53; 95%CI 0, 1) and Engel (k0.50; 95%CI 0.21, 0.78).Conclusions: The current body of literature reporting seizure outcome based upon Engel's system is likely to have an acceptable degree of inter-rater agreement in children as well as adults, while it is even better for the ILAE system. Although most outcomes using the Engel system have been classified retrospectively, the ILAE system has been advocated for prospective studies. The availability here of data on preoperative seizure days also supports its uptake for retrospective use. Assessing seizure outcome following VNS implantation using either system may have an unacceptably low degree of inter-rater agreement; further exploration of other classifications is warranted.

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EFFICACY AND SAFETY OF PERAMPANEL, AN AMPA RECEPTOR ANTAGONIST, AS AN ADJUNCTIVE THERAPY IN A PHASE III STUDY OF PATIENTS WITH REFRACTORY PARTIAL-ONSET SEIZURES

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Rationale: Perampanel (E2007) is a selective, non-competitive alpha-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid (AMPA) antagonist that was effective in several animal seizure models. Perampanel was well tolerated in preliminary Phase II trials and is being evaluated as an add-on therapy for patients with refractory partial seizures in a Phase III program. This report describes the results of the first large multinational Phase III randomized, placebo-controlled trial demonstrating the efficacy and safety of perampanel (2-8 mg/day) as add-on therapy for refractory partial seizures.Methods: Subjects were 12-72 yrs old with partial seizures with/without secondary generalized seizures treated with 1-3 concomitant AEDs. Subjects were randomized to treatment with once-daily perampanel 2, 4, or 8 mg/day, or to placebo. Following a 6-week Baseline Phase, patients entered a 19-week Treatment Phase (6- week titration and 13-week maintenance). The primary endpoint was median percentage change in 28-day seizure frequency in the Maintenance Period relative to Pre-randomization. Secondary endpoints included responder rate (subjects with at least 50% reduction in seizure frequency during Maintenance Phase relative to Pre-randomization). Safety and tolerability were secondary objectives. Results: 712 subjects (49% male; 65% Caucasian; mean age 34 yrs) were randomized in 25 countries in Europe and Asia-Pacific regions to treatment with 2 mg (n=180), 4 mg (n=174), and 8 mg (n=171) perampanel/day, or to placebo (n=187). Median seizure frequency change for the ITT population was -16.3% (p=ns), -28.6% (p=0.003), and -33.5% (p<0.001) in the 2, 4, and 8 mg perampanel/day groups, respectively, versus - 13.8% with placebo. Responder rates were 20.9% (p=ns), 28.6% (p=0.009), and 34.9% (p<0.001) in the 2, 4, and 8 mg perampanel/day groups, respectively, versus 17.6% with placebo. The most frequent treatment-emergent adverse events (TEAEs) occurring in e”10% of subjects in any group (2, 4, or 8 mg perampanel/day, or placebo) were dizziness (10.0%, 16.3%, 26.6%, and 9.7%, respectively), somnolence (12.2%, 9.3%, 16.0%, and 6.5%, respectively), and headache (8.9%, 11.0%, 10.7%, and 8.6%, respectively). There were no unexpected TEAEs and few or no changes in vital signs, laboratory tests or ECGs were observed in treatment groups compared to placebo. 623 subjects completed the study; the number of patients who withdrew due to adverse events was low (10, 5, and 11 subjects in the 2, 4, and 8 mg perampanel/day groups respectively, versus 6 with placebo). Serious TEAEs were infrequent and were not higher with perampanel treatment compared to placebo (3.3%, 3.5%, and 3.6% with 2, 4, and 8 mg perampanel/day, respectively, versus 4.9% with placebo). Conclusions: This study confirms the efficacy and safety of perampanel 4 and 8 mg/day doses as add-on therapy for partial-onset seizures. The results also help to identify the potential lower dose range for treatment. (Support: Eisai Inc)

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THE SOLUBLE EPOXIDE HYDROLASE REGULATES HIPPOCAMPAL NEUROINFLAMMATION IN ADULT MICE AFTER PILOCARPINE-INDUCED STATUS EPILEPTICUS

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Rationale: Status epilepticus (SE) and other potential brain insults may lead to the development of temporal lobe epilepsy via the induction of neuronal network alterations in the hippocampal formation. Neuroinflammation identified in epileptic focus of humans and experimental animals has been suspected to participate in the formation of neuronal cell death, reactive gliosis, aberrant neurogenesis and synaptic reorganization. Recent studies with hypoxia and ischemic preconditioning experiments have shown that the increase in the cerebral level of epoxyeicosatrienoic acid (EET), a fatty acid signaling molecule, may confer protection from ischemic stroke. Soluble epoxide hydrolase (sEH) is a key enzyme for metabolic conversion of EETs into their less active form, DHET. By using pharmacologic inhibitor or genetic deletion, previous studies have demonstrated that inhibition of sEH attenuated the vascular and neural injury induced by cerebral ischemia, suggesting that this enzyme might be a novel target in treatment of stroke. However, it remains unknown whether sEH is involved in neuroinflammation-related epileptogenesis. The present study aimed to examine 1). the temporal and spatial distributions of sEH in mice with pilocarpine-induced SE, 2). the corresponding change in inflammatory cytokines, and 3) the effect of sEH inhibitor on local neuroinflammation following SE. Methods: Pilocarpine (325 mg/kg) was intra-peritoneally administered to induce SE in adult male C57BL/6 mice. The coronal brain sections of SE mice obtained at 1, 3, 7, 14, 21, 28 and 35 days post-SE (n=4 in each group) were analyzed for sEH expression by immunohistochemistry with anti-sEH antibody. The hippocampal proteins were extracted for measuring the expression of sEH and cytokines (IL-1, IL-6) by western blot and ELISA, respectively. In another experimental group, daily injection of the sEH inhibitor adamantylureido- dodecanoic acid (AUDA, 20 mg/kg, i.p.) was given at days 1 ~ 6 after SE induction, and then the mice were sacrificed at day 7 for measuring the cytokine expression.Results: Doublelabeling staining with an antibody against glial fibrillary acidic protein (GFAP) clearly revealed sEH immunoreactivity in astrocytes in the molecular layer of CA1, CA3 and dentate hilus in SE mice. Compared to control mice, the sEH expression was higher at day 7 after SE. The inflammatory cytokines (IL-1, IL-6) were significantly increased after SE, and the IL-1² and IL- 6 expressions peaked at day 7. Moreover, the expressions of IL-1 and IL-6 were dramatically decreased in the mice treated with AUDA in comparison with those treated with vehicle.Conclusions: Our findings suggest that sEH is involved in SE-induced neuroinflammation under SE mouse model.

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COMPARISON OF P3 RESPONSES BEFORE AND AFTER SURGERY IN TLE PATIENTS USING CD ANALYSIS

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Rationale: To better characterize changes in cognitive function resulting from surgery, EEG was recorded in patients with temporal lobe epilepsy (TLE) before and after surgery as they performed an oddball task. Two types of analyses compared function pre- and post-surgery: event-related potential (ERP) analyses focusing on the P3 component, and a frequency analysis using complex demodulation (CD).Methods: Five TLE patients (2 females, mean age 30.1 ± 6.5 years, all right

handed) participated in the study. Patients took a various number of anti-epileptic drugs (AED), with two patients taking one AED, two patients taking two AEDs, and one patient taking three AEDs. Seizure frequency prior to surgery also varied such that it was daily in one patient, weekly in two patients and monthly in two patients. All patients were seizure free after surgery. Epileptic foci were localized to the left hemisphere for two patients and to the right hemisphere for three patients. All patients were hospitalized for pre-surgical monitoring, epilepsy surgery and post-operative controls in the Tokyo Medical and Dental University Medical Center. Pre-surgery examinations were conducted one to two months prior to surgery (mean = 28.0 days), and post-surgery examinations were conducted between one to four months after surgery (mean = 42.8 days). EEG was recorded during an auditory oddball task from four midline locations (Fz, Cz, Pz and Oz). Stimuli consisted of 1000Hz pure tones (frequent; 80% of trials) and 1050Hz tones (rare; 20% of trials). A minimum of 20 good deviant trials were included in each participant's average waveform. Participants were instructed to count the number of rare stimuli while watching silent cartoons. For ERP analyses, peak amplitude, mean amplitude and peak latency were evaluated at each electrode 400-530ms post-stimulus onset. Frequency analyses were performed using CD. Induced EEG responses were first divided into 0.25 Hz bins (ranging from 0–50 Hz), and amplitude was then evaluated for each bin. EEG and EOG (electrooculographic) data were filtered from 0 – 50 Hz. Statistical analyses included twoway repeated measures ANOVAs. Results: P3 grand average waveforms are shown in Fig. 1. There was no significant difference among them. CD analyses of induced EEG responses revealed that delta (½-3 Hz) and theta (4-7 Hz) activity increased after surgery, whereas fast activity (25-40 Hz) decreased (shown in Fig. 2).Conclusions: Although there were no significant differences in the pre- and post-surgery P3 grand averages, CD analyses revealed increased delta and theta activity as well as decreased fast activity after surgery. CD analysis may thus be a useful method for observing cognitive function.

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PERFORANT PATHWAY STIMULATION IN FREELY-MOVING RATS: THRESHOLD FOR HIPPOCAMPAL NEURODEGENERATION

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Rationale: Whether individual seizures cause brain cell death in humans or animal models is debated. One hypothesis is that each seizure produces subtle cell loss. The alternate hypothesis is that one event, such as a single, prolonged seizure, is responsible for most, if not all, epilepsyassociated neuron loss. Nonetheless, each theory is supported by published studies. Perforant pathway stimulation causes seizures, significant neuronal injury, and spontaneous epilepsy in rodents. However, the minimum duration of stimulation-induced seizures required to produce brain cell death in naïve rodents, and precisely which hippocampal neurons are the first to die, remain unresolved issues. Methods: Bilateral perforant pathway stimulation, comprised of continuous 2 Hz paired-pulse stimuli with a 40 ms interpulse interval, along with one 10 sec epoch of 20 Hz single pulses each minute, was applied to awake, freely moving Sprague-Dawley rats. Concurrent recording directly from the hippocampal granule cell layer allowed us to monitor hippocampal activity in real-time, and control the duration of stimulation for each animal (10 seconds to 40 minutes), individually. At the end of each stimulation epoch, isoflurane anesthesia was administered to rapidly terminate seizure activity. Seven days after stimulation, animals were perfusion-fixed with 4% paraformaldehyde. 40 ¼m-thick coronal brain sections were mounted on glass slides, dehydrated, stained with FluoroJade-B (FJB), and analyzed with fluorescence microscopy to ascertain neuronal degeneration. Results: Perforant pathway stimulation induced and maintained hippocampal seizures throughout the duration of each stimulation epoch. The minimum stimulation duration that produced FJB-detectable neurodegeneration was 40 minutes. FJB-stained neurons were limited to the dentate hilus of the dorsal hippocampus. Conclusions: These data rebut the hypothesis that a brief, individual seizure causes brain cell death in rats. We did not see any evidence of neurodegeneration produced by stimulation durations of up to and including 30 minutes. Neurons in the dentate hilus are among the first to die after perforant pathway stimulation under urethane anesthesia and are some of the most vulnerable to kainate- and pilocarpine-induced seizures. These data confirm these observations, and demonstrate that hilar neurons are the first neurons to succumb to perforant pathway stimulation-induced seizure activity in awake rats.

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STRUCTURAL ALTERATION IN BBB AND MDR-1 PROTEIN EXPRESSION IN TISSUE OF PEDIATRIC PATIENTS WITH PARTIALIS CONTINUA EPILEPSIA

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Rationale: Approximately 30% of patients with epilepsy develop intractable seizures [i.e., seizures persist despite accurate diagnosis and carefully monitored treatment with antiepileptic drugs (AEDs. The mechanisms underlying multidrug resistance (MDR) in epilepsy are still elusive. Some risk factors have been identified in patients, (i.e., time of onset of epilepsy, type and etiology of seizures, and number of seizures before the start of the treatment), the form of chronic progressive epilepsia partialis continua (EPC) of childhood is diagnosed how Rasmussen's encephalitis upon histologic confirmation. It remains a rare and not easily diagnosed syndrome for which no etiology has been ascribed. The purpose of this study was to examine the structural alterations in BBB and the immunological and cellular characteristics in the brain obtained after hemispherectomy in patient with EPC, as well as to know the Mdr-1 expression in the same tissue. Methods: Fourteen cases were analyzed from epileptic tissue from cerebral cortex, obtained from patients with Rasmussen's encephalitis . The tissue were processing to be including in paraffin y a block serial of each section was frozen and cut at criostate to -20 C. All blocks of tissue (paraffin and frozen) were cut and 12 um. Other tissue block was used to immunofluorescence stain in criostat sections to -20 C, for electronmicroscopic study the tissues were fixed in Karnovski solution and one samples were collected in vial free of RNAasas and rapidly frozen at N2 liquid to identify Mdr-1 by Western blot technique. Results: The results showed damage in the blood brain barrier that coexisted with an increase in the expression of the Mdr-1 in vascular endothelia, astrocites and neurons close the vessel mainly microvessel in the epileptic focus in gray matter and less in the white matter and several grade of inflammatory process.Conclusions: The results indicate that the degenerative process in this type of patient has an evolutionary course with the advance of the tissue damage, in addition are associated with alterations in the elements of the BBB and an increase in the expression of protein the transporting Mrp- drug that probably contributes to make but these patients refractory. This study was supported by the National institute of Science and Technology GDF(IPFTU-08-27), National Council for Sciences and Technology of Mexico (grants S52955-M)

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NONINVASIVE ULTRASONIC NEUROMODULATION FOR STATUS EPILEPTICUS: PRELIMINARY OBSERVATIONS

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Rationale: Status epilepticus (SE) that is refractory to anti-epileptic drugs typically has a poor prognosis, but patients may recover well if seizures can be terminated. We have recently developed and published novel methods for using transcranial pulsed ultrasound (TPU) to stimulate brain activity (Tufail et al, 2010) . TPU can also synchronize intact hippocampal oscillations in high-frequency sharp-wave and gamma bands without producing damage. Since epileptic seizures have been attributed to runaway excitation in certain brain circuits including the hippocampus, we hypothesized TPU can provide an interference stimulus source capable of terminating aberrant activity observed during electrographic seizures. Thus, TPU may represent a brain stimulation method capable of providing rapid relief of SE during neurological emergencies.Methods: We studied the acute effects of transcranial US stimulation on healthy and kainic acid (KA) induced status epilepticus mice. We also studied the effect of US stimulation in freeze lesion models of polymicrogyria (cortical dysplasia). Efficacy of seizure control was measured by continuous fine wire EMG, intracranial extracellular recordings and monitoring duration of behavioral signs of seizure activity. Functional activity maps were constructed using antibodies against c-fos and compared before and after US stimulation of KA-induced status epilepticus mice.Results: Low-intensity continuous wave ultrasound (0.35 MHz) was applied for 2 to 10 seconds during SE. TPU significantly attenuated electromyographic seizures, as well as reduced the duration and severity of SE as indicated by Racine stage monitoring. Mice tolerated the TPU treatment procedures well. Conclusions: Our preliminary results suggest the feasibility of using ultrasonic neuromodulation for the acute treatment of status epilepticus. TPU holds the potential to be a viable noninvasive therapeutic paradigm for refractory status epilepticus. Reference: Transcranial pulsed ultrasound stimulates intact brain circuits. Tufail Y, Matyushov A, Baldwin N, Tauchmann ML, Georges J, Yoshihiro A, Tillery SI, Tyler WJ. Neuron. 2010 Jun 10;66(5):681-94

2.386

MULTIPLE MECHANISMS RAPIDLY REGULATE TONIC GABA CURRENTS IN CULTURED RAT HIPPOCAMPAL NEURONS

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Rationale: Tonic activation of GABA_A receptors provides a potent inhibitory mechanism for hippocampal neurons. Chronic cellular and molecular changes seen in epilepsy are known to affect tonic inhibition. Less is known about the mechanisms regulating tonic inhibition over short time periods. Methods: Tonic GABA currents were measured from cultured rat hippocampal neurons using whole cell patch clamp techniques to evaluate how endogenous tonic currents are affected by (1) transient increases in extracellular [GABA], (2) depolarization during GABA application, or (3) depolarization of presynaptic terminals with 12 mM K+. Experiments were performed with symmetrical Cl- concentrations under conditions to isolate GABA_A receptor mediated currents. Rapid solution exchanges were produced with a microperfusion system.Results: Tonic currents due to endogenous GABA were measured before and after application of exogenous GABA (1 ¼M). Tonic currents were reduced by 25±9% when measured 5 s after GABA application (mean±SEM, $p<0.05$, n=11 neurons). Reductions in driving force due to GABA-induced shifts in E_{GABA} (-0.8±0.7 mV to –9.2±1.8 mV, n=8) accounted for this reduction in tonic current. Transient depolarization to +40 mV during the application of exogenous GABA converted the reduction in tonic current into a potentiation, tonic currents measured 6 s after repolarization were increased by 68±13% (n=11, $p<0.01$). When cells were depolarized during GABA application E_{GABA} shifted from –1.2±0.9 mV to +3.0±0.3 mV (n=8), this shift in E_{GABA} was too small to account for the observed potentiation (theoretical E_{GABA} shift required to produce this potentiation would be +41±8 mV, $p<0.01$). The voltage-dependent potentiation of tonic GABA currents represented postdepolarization potentiation (PDP), an intrinsic GABA_A receptor property. Reducing vesicular GABA release with zero extracellular Ca2+/EGTA did not affect tonic current density in cultured hippocampal neurons. To prevent vesicular release of GABA, cultures were treated with the vesicular H+-ATPase inhibitor concanamycin A (conA). Tonic current in conA-treated neurons was no different than that in control neurons (-58±12 vs. -39±4 pA, $p=0.24$, n=5-7). In conA-treated cells, transient application of 12 mM K+ to depolarize presynatptic terminals increased tonic current to –140±50 pA ($p<0.05$, n=5). The K+-induced increase in tonic current was reversibly inhibited by SKF89976a, indicating that this was due to GABA release mediated by reversal of GABA transporter type 1 (GAT1).Conclusions: Tonic GABA currents are rapidly regulated by GABAinduced changes in intracellular Cl- concentration, PDP of extrasynaptic GABA_A receptors, and nonvesicular GABA release. These mechanisms may influence tonic inhibition during seizures when neurons are robustly depolarized and extracellular GABA and K+ concentrations are elevated.

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RESISTANCE TO CLASSICAL ANTIEPILEPTIC DRUGS IN THE MTLE MOUSE: A MODEL OF MESIAL TEMPORAL LOBE EPILEPSY TO EXPLORE NEW MECHANISMS OF ACTIONS?

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Rationale: Mesiotemporal lobe epilepsy (MTLE) is one of the most difficult form of epilepsy to treat as patients are often resistant to antiepileptic drugs (AEDs) and, when possible, surgical resection appears as the only effective therapy. This resistance is far from being understood and identification of new active compounds requires the development of new animal models. Methods: Recently, both morphological and electroclinical features of MTLE were shown to be mimicked following a unilateral injection of kainic acid (KA) in the dorsal hippocampus of adult mice. Here epileptogenesis and appearance of spontaneous focal hippocampal paroxysmal discharges (HPD) were explored by EEG with telemetry. Our initial data suggested that established HPD were not suppressed by classical AEDs. Here we examine the effects of new AEDs, at several doses, on the spontaneous occurrence of HPD by EEG.Results: EEG telemetric recording showed a progressive appearance of HPD with stabilization 3 weeks post-status and expression of 40 HPD/h. Injection of classic AEDs (valproate, carbamazepine and lamotrigine) fails to suppress HPD in a dose-dependent way. Indeed only high doses are effective (400, 100 and 90mg/kg respectively) and are associated with modifications of the general behavior and/or EEG basal activity. A dose-dependent suppression of HPD was however observed with new AEDs: levetiracetam (100, 400, 800, 1000 mg/kg), vigabatrin (10, 50, 100, 200mg/kg), pregabalin (10, 50, 100 mg/kg) and also with diazepam (0,5, 1, 2, 3 mg/kg) without obvious behavioural or EEG side-effects. When diazepam or levetiracetam were administered daily (4 and 1600 mg/kg/day, respectively), their suppressive effects on HPD progressively vanished within 5 days. A significant aggravation of HPD was observed on the first day of a wash-out period.Conclusions: Together these data suggest this mouse model of MTLE provides a new valuable tool to

study the potential effects of new AEDs and development of tolerance directly by assessing their effect on the expression of focal hippocampal discharges.

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EPILEPSY AFTER FEBRILE SEIZURES: TWINS SUGGEST GENETIC INFLUENCE

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Rationale: Although numerous studies have shown a history of complex febrile seizures (FS) will increase the risk of epilepsy, the role of genetic factors is unclear. Previous studies have suggested that a significant family history of febrile seizures may not be a risk factor for developing epilepsy. This study was carried out to evaluate the genetic epidemiology of FS in a large cohort ascertained from three large population-based twin registries.Methods: Information on history of seizures was obtained either by mailed questionnaire or telephone interview from 81, 798 twins included in three population-based twin registries located in Denmark, Norway and the United States. Seizures were validated by personal and/or parental interviews, and medical records when available. FS type was classified by epileptologists to distinguish simple or complex (including status epilepticus) FS. The proportion of twins with FS classified by type, who later developed epilepsy, was determined. Results: Histories of FS were validated in 1049 twins in 899 pairs. Of these, 2.5% (16/641) with a history of simple FS alone, 11.3% (14/124) with a history of complex FS and 22.2% (16/72) of those with at least one episode of febrile status epilepticus went on to develop epilepsy. The percentage of those who developed epilepsy whose FS type could not be classified was 14.2% (20/211). In 40.6% of the 97 twin pairs where one pair member had a FS and went on to have epilepsy, a history of seizures was also verified in the cotwin. This included 17/24 (70.8%) monozygotic pairs and 10/41 (24.4%) dizygotic pairs. Among individuals that developed epilepsy after FS, 21.1% had only simple FS, 18.4% had complex FS (without status epilepticus) and 21.1% had febrile status epilepticus. Conclusions: These results are consistent with previous findings regarding the association between FS and the later risk for epilepsy. This is not limited to FS semiology. The increased frequency of seizures in the cotwin of monozygotic pairs with FS who went on to develop epilepsy suggests that genetic factors may play a significant role in its later development. Whether these families represent patients with GEFS+ or other known syndromes are presently unclear and requires further clinical and molecular evaluation.

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NORMAL VIGILANCE CYCLING COMPROMISES THE ABILITY OF EEG TO PREDICT SEIZURES

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Rationale: Numerous measures computed from the EEG have been proposed for detecting preictal states in epilepsy, but few perform better than chance when tested on prospective data. Multivariate measures of coherence across brain areas have shown some seizure-predictive ability, but with poor specificity (i.e., high false positive rate). Sleep-wake state is one factor known to bias the number of false positives generated by seizure prediction algorithms (SPAs). It is to be expected that switching between different normal states of vigilance (SOV) is accompanied by changes in coherence; however, little is known about the effect of normal vigilance cycles on the dynamics of SPA measures, and on seizure likelihood. We have previously studied the effect of SOV on seizures in a rodent model of temporal lobe epilepsy. Here we use this model to test the effect of SOV changes on measures of EEG coherence, and compare values to the preseizure period.Methods: Tetanus toxin implanted in the hippocampus of rats generated spontaneous, intermittent seizures for weeks after a latency of 2-4 days. Seizures were detected and verified using video-EEG. Univariate EEG power in different frequency bands, along with head acceleration, was computed from cortex and hippocampus and used to discriminate SOV—i.e., NREM sleep, REM sleep, quiet wake (QW) or active wake (AW)—in sequential 10s epochs. Multivariate measures of coherence between pairs of EEG channels, specifically the linear cross-correlation peak r² and the broadband Hilbert phase coherence R, were computed in 10s epochs and averaged over all channel combinations. Distributions of r² and R were estimated for different SOV in the post-implant latent period prior to any seizures, and compared with a 5 min period prior to each seizure after the development of spontaneous seizures.Results: Measures of EEG coherence were found to vary with SOV in epileptic rats. The most significant difference ($p<0.01$) was a surge in value during AW behaviors such as exploratory motion. Differences between REM, NREM, and QW were not as distinctive for the chosen measures; furthermore, the preseizure period (n = 30 seizures) could not be distinguished from REM, NREM, and QW. Finally, the SOV during the preseizure period was predominantly scored as REM or NREM sleep.Conclusions: Not only do measures of EEG coherence offer poor contrast between the preseizure period and normal vigilance cycles, but changes in coherence may frequently track transitions to some normal but more seizure-permissive state (e.g., slow wave sleep or arousal) rather than a unique preictal state. Neither of the above facilitates the development of accurate seizure prediction algorithms. However, it is possible that specific choices made in this study— for instance, averaging of measures over all available channels or the use of broadband instead of band-limited coherence—may have contributed to the lack of specificity. Nevertheless, it is clear that, at a minimum, SPAs must incorporate adaptive state-dependent corrections to achieve the level of performance desirable in clinical use.

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USE OF RUFINAMIDE IN ADULTS WITH EPILEPSY

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Rationale: Rufinamide (RFM) was licensed for use in the treatment of Lennox-Gastaut Syndrome (LGS) in 2008. The present chart review was conducted to assess the safety, efficacy, and retention when rufinamide is used off-label in adults with refractory epilepsy other than LGS, and to compare to on-label use.Methods: We conducted a retrospective chart review of the first 48 adult outpatients prescribed RFM at the Columbia University Comprehensive Epilepsy Center. This project is part of the Columbia AED Database, which funded by several pharmaceutical companies, including Eisai, the distributer of rufinamide.Results: The mean was age 41, ranging from 18 to 70 years. Patients consisted of 13 (27%) with Symptomatic Generalized Epilepsy, including 6 LGS, 20 (42%) with Primary Generalized Epilepsy (PGEN), 13 (27%) Focal Epilepsy, and 2 (4%) Focal and PGEN. We looked at drug retention at six and twelve month time periods, where retention was defined as the number of patients on RFM for the time period or greater, out of the total number of patients, excluding those on the drug for less than the time period and still on it. At six months, 30 (71%) patients remained on RFM and at twelvemonths, 9 (29%) remained. On-label patients had retentions of 4/6 and 1/3, with offlabel patients showing similar retentions of 26/36 (72%) and 8/28 (27%) for six and twelve months, respectively. 16

(33%) patients reached the recommended dose of 3200mg or higher. 17 (35%) experienced adverse effects attributed to RFM that led to dose change or discontinuation. Dizziness (6.3%) and GI upset (6.3%) were the most common side effects. In the 38 patients with documented seizure frequencies, 8 (21%) experienced a 50% or greater decrease in seizure frequency (responders). Among responders, improvement occurred most often at 1600mg/day (4 patients), with maximum dose at 3200mg/day (3), and final dose at 1600mg/day (4). Of the 6 LGS patients, 1was a responder. 7 of the 32 (22%) off-label patients were responders. Seizure worsening (>50% increase in seizure frequency) while on RFM (often while tapering off another AED) occurred during on-label use in 1/6 cases, and during off-label use in 10/32 patients. All seizure types seem to respond similarly, though numbers were very small for this analysis.Conclusions: The results of this study indicate that rufinamide can be a useful adjunctive agent for adult patients with refractory epilepsy, both on- and off-label, regardless of epilepsy syndrome. Total retention on RFM was high at six months (71%), dropping considerably by 12 months (29%). Only a third of patients reached the maximum recommended dose, with maximum benefit most commonly seen at 1600 mg/day. Adverse effects were mild, transient, and consistent with previous studies. Further studies are needed to determine the best candidates for RFM, but rufinamide appears to be effective in some patients with a variety of epilepsy syndromes.

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DEFINITION OF THE NEUROLOGICAL PHENOTYPE ASSOCIATED WITH DUP (X)(P11.22-P11.23)SYNDROME

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Rationale: To describe in detail the neurological features of nine patients (both familial and sporadic) with mental retardation, speech delay, electroencephalogram (EEG) abnormalities and facial dysmorphisms carrying the recently reported microduplication at Xp11.22-11.23 (Am J Hum Genet 2009; 85:394-400.Methods: Clinical and neurological examination, brain magnetic resonance imaging (MRI) (except two patients), EEG and a neuropsychological assessment specific for language disturbances were performed in nine patients with microduplication at Xp11.22-11.23 disclosed by comparative genomic hybridization (CGH) array. Six patients were familial cases belonging to three unrelated pedigrees and three were sporadic cases.Results: The patients had the following characteristics: mild dysmorphic facial features, mental retardation with a moderate-severe global language deterioration; wake and sleep EEG showing epileptiform discharges especially activated during sleep or electrical status epilepticus during slow sleep (ESES) in younger cases; negative brain MRI. Conclusions: The main clinical features of this new chromosomopathy, i.e. Xp11.22-11.23 microduplication, are mild facial dysmorphisms, electrical status epilepticus during slow sleep (ESES) in childhood and a mental retardation mainly involving language function. We are unable to discriminate whether speech impairment in adult cases results from a past ESES no longer evident in adulthood as in our familial cases, but nonetheless able to cause local damage, impairing plastic changes associated with language learning (Epilepsia 2009;50:4-8) (Clin Neurophysiol 2000;111:S94-S102) (Epilepsia 2006;47:40-3) (Brain Res Bull 2003; 62: 143-50), or is due to abnormal brain expression of a dosage-sensitive gene contained within the duplication region ((Am J Hum Genet 2009; 85:394- 400).

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PRESURGICAL PLANNING OF INTRACRANIAL GRID PLACEMENT FOR IMPROVEMENT OF SEIZURE CONTROL.

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Rationale: Investigations of refractory epilepsy using intracranial electrodes remains a highly invasive procedure with significant risks related to size of craniotomy and distribution of implanted electrodes. A priori definition of epileptogenic zone is crucial to optimize spatial EEG sampling via accurate electrode placement and ultimately confirm extent of resection for seizure control. A novel technique to mediate this risk using improved neuronavigation models of individual brains is indicated. Methods: In patients with implanted strip or grid electrodes for EEG monitoring, presurgical MRI data was imported into Curry Neuroimaging Suite 7 (CNS) (Compumedics Neuroscan, Charlotte, NC, USA) and used for constructing head and cortex models. A novel interactive, semi-automatic procedure was employed to define these electrode positions. The operator, able to freely move and rotate individual grids and strips, had certain parameter constraints automatically enforced by the software. These constraints included interelectrode distances (20, 10 and 5mm), an orthogonality constraint between grid rows and columns, and electrodes were required to reside on a smoothed representation of the cortical surface. Results: Planned electrode positions were exported as high intensity points on T1 scans for visualisation using frameless stereotactic registration of the Stealth Neuronavigation System (Medtronic, Louisville, CO, USA). Confirmation of electrode placement intraoperatively was performed using neuronavigation probe sampling specific points. Validation of preplanned electrodes was confirmed from models using high resolution CT.Conclusions: This technique represents a novel approach to objective placement of intracranial electrodes, reducing the impact of inadequate EEG spatial sampling from misplacement. It has the potential to more accurately define an epileptogenic focus prior to resection and therefore lead to improved seizure control.

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EMERGENT EEG IN THE EMERGENCY DEPARTMENT IN PATIENTS WITH ALTERED MENTAL STATES

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Rationale: The electroencephalogram (EEG) is underused or not available in the Emergency Department (ED). Criteria for EEG in the ED have not been established. This study sought to determine whether EEG performed within 30 minutes of referral by an ED physician helps establish diagnosis and/or changes management, and which clinical features/diagnoses are useful in selecting patients for ED EEG. The reliability of an abbreviated 5 min EEG was explored.Methods: Single-center prospective cohort intervention study one day/week, of sequentially referred adult patients presenting with clinical seizure activity or altered mental status (AMS). Standard EEGs (20 minute 16-channel) were performed by an EEG technician using a commercially available cap. EEGs were graded for quality and interpreted by an epileptologist, immediately reported to the ED physician and a utility survey completed. The inter-EEG reliability of quality and interpretation of the 20 min EEG vs. a pre-specified 5 min segment of each EEG was measured using the Kappa Coefficient.Results: Over 1 year, 82 patients (mean age 58.1 ± 2.0 years) underwent ED EEG. Tonic clonic seizure activity had occurred in 33%. Mean time for EEG setup was 13.1 ± 6.2 min. Time from start of EEG setup to arrival of the epileptologist was 55.0 ± 25.7 min. The EEG result was reported to

ED staff in 4.3 ± 2.7 min. EEGs were categorized as normal (39.0%), showing diffuse abnormalities (± epileptiform discharges)((31.7%), focal abnormalities (± epileptiform discharges)(17.1%), electrographic seizures (1.2%) or uninterpretable (11.0%). EEG assisted the diagnosis in 51%, changed ED management in 4% and would be ordered again if EEG was available in 46%. Positive utility of EEG was significantly associated with etiology of AMS (toxicologic, psychiatric and endocrine/metabolic causes vs. other causes) (P=0.001) and sudden onset of AMS (P=0.04). Independent predictors of whether ED EEG would be ordered if available were witnessed seizure activity (P=0.01), absent prior head trauma (P=0.001) and survey respondent being a physician assistant (vs. MD) (p=0.008). The 5 min EEG (vs. 20 min EEG) presented substantial agreements on waveform shape/amplitude (Kappa=0.78), presence of artifact (Kappa=0.75) and on interpretation categories (diffuse or focal abnormalities, normal, seizure and uninterpretable) (all Kappa levels > 0.70).Conclusions: Rapid availability of standard 20 min full-montage EEG in the ED is feasible and helps establish a diagnosis in about half of patients with AMS, but rarely changes management. While witnessed seizure activity and absence of head trauma are most likely to prompt a request for ED EEG, non-neurologic causes of AMS and sudden onset are more likely to be associated with positive benefit. Our results suggest that an abbreviated 5 min full-montage EEG presents adequate reliability which may improve acceptance and use of EEG in the ED.