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35th International Epilepsy Congress
2-6 September 2023 | Dublin, Ireland

Congress Abstracts

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35th International Epilepsy Congress

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Oral Presentations

Adult Epileptology

15:30-16:30

Monday, 4 September

The Auditorium

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Resilience and epilepsy: impact on psychosocial factors and stigma

M Tombini[1,2], F Narducci[1,2], L Ricci[1,2], M Boscarino[1,2], B Sancetta[1,2], L Quintiliani[3], J Lanzone[4], M Straffi[1], V Di Lazzaro[1,2], G Assenza[1,2] [1]University Campus Bio-Medico, Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, Rome, Italy, [2]Fondazione Policlinico Universitario Campus Bio-Medico, Unità di Neurologia, Rome, Italy, [3]Fondazione Policlinico Universitario Campus Bio-Medico, Psicologia Clinica, Rome, Italy, [4]Istituti Clinici Scientifici Maugeri IRCCS, Neurorehabilitation Unit of Milan Institute, Milan, Italy

Purpose: Resilience is defined as “a dynamic process that includes a positive adaptation in the context of significant adversity”. The aim of our study was to evaluate the resilience, through a dedicated scale, in a group of people with epilepsy (PWE) and its impact on psychosocial factors, in particular the presence of feelings of stigmatization.
Method: We consecutively enrolled 204 adult PWE (128 F/72 M; mean age 42,4 y). 107 were seizure free (SF, 53,5%) and 93 not-seizure free (NSF, 46,5%). All subjects completed at baseline (T0) the Resilience Scale (RS-14) and questionnaires for the assessment of depressive symptoms, anxiety and quality of life: respectively, Beck Depression Inventory-II (BD-II), Generalized Anxiety Disorder-7 (GAD-7) and QOLIE-31 (Q31). Finally, 82 patients were followed up prospectively and re-evaluated after 6-12 months (T1); at follow up they also completed the Stigma Scale of Epilepsy (SSE) for the assessment of the stigma associated with epilepsy. Therefore, we correlated RS-14 values with all psychosocial aspects at both times, in particular feelings of stigmatization.
Results: The results showed for the RS-14 a significant direct correlation at both times (T0 and T1) with the Q31 ($p < 0.001$) and inverse with the depressive and anxiety symptoms, as evaluated with BDI-II ($p < 0.001$) and GAD-7 ($p < 0.001$). Finally, for the first time, a significant inverse correlation was evidenced between RS-14 at baseline and the levels of stigmatization, assessed with SSE at follow up ($p=.015$). No correlation was observed between resilience/stigma and seizure frequency at both times (T0 and T1) as well as changes of seizure rate or clinical outcome.
Conclusion: Our study showed that in PWE depressive symptoms, anxiety and quality of life were significantly associated with resilience, which was found to be able to prospectively influence the perception of stigma related to epilepsy more than seizures.

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An internationally derived core outcome set for adult epilepsy treatment trials: the

EPSET project

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Purpose: A Core Outcome Set (COS) is a standardised list of outcomes that should be reported as a minimum in all trials. It is developed using consensus methods to ensure that it includes what is important to patients as well as professionals. In epilepsy, the choice of outcomes measured varies widely among existing studies, particularly in randomised controlled trials (RCT). COS facilitate the undertaking of trials that are relevant to patients and health services and help standardise trial methodology.
We have developed an internationally derived COS specific to adult epilepsy treatment trials.
Method: We performed a rapid review of the qualitative literature exploring experiences of people with epilepsy to identify concepts that map to potential measurable outcomes. We also reviewed outcomes already measured in phase 3 and 4 epilepsy specific RCTs, to generate an outcome long-list.

In collaboration with the ILAE Big Data Commission and an international group of healthcare providers, researchers, and people with epilepsy we have performed a grouping and rationalisation process and taken 42 individual outcomes to a two-stage, online Delphi survey followed by consensus meeting.
Results: 490 people with epilepsy, their representatives, healthcare professionals and researchers have completed the Delphi surveys in 7 languages, representing the global perspective. Inconclusive outcomes were discussed, and the final outcomes ratified at international online consensus meeting. The ratified COS includes a minimum set of seizure and non-seizure outcomes, that should be measured and reported as a minimum in all future clinical trials. Future work should identify the most appropriate measurement instruments to capture each item in the COS.
Conclusion: The EPSET Project has identified a COS for adults with epilepsy and derived international consensus. This will ensure that meaningful outcomes are measured in future clinical trials, that the results of trials are relevant to people with epilepsy and facilitate systematic review and meta-analysis.

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Impact of Fenfluramine on drop seizure frequency in adults or dose-capped patients with Lennox-Gastaut Syndrome: comparative analysis of clinical trial data

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Purpose: Treatment for Lennox-Gastaut syndrome (LGS) is individualized and may evolve as the syndrome persists and changes into adulthood. Patients weighing ≥37.5kg (ie, most adults) have their doses capped at 26mg/day and therefore receive doses ≤0.7mg/kg/day. Here, we evaluate fenfluramine treatment on drop seizure frequency (DSF) in adults and patients who were dose-capped at 26mg/day in a randomized clinical trial (RCT) or open-label extension (OLE) for LGS.
Method: After 4-weeks' baseline in the RCT, LGS patients (2-35 years) were randomized to fenfluramine 0.7mg/kg/day (maximum, 26mg/day), fenfluramine 0.2mg/kg/day, or placebo for 2 weeks (titration) and 12 additional weeks. Eligible patients continuing into the OLE started on fenfluramine at 0.2mg/kg/day after a blinded 2-week taper. After 1 month, doses were titrated to effect/tolerability.
Results: In the RCT, 76 adults (≥18-35 years) and 187 children/adolescents (2-17 years) were randomized to fenfluramine 0.7mg/kg/day (n=25 and 62, respectively), fenfluramine 0.2mg/kg/day (n=25 and 64), or placebo (n=26 and 61). Among both adults and children/adolescents, median DSF reduction from baseline was numerically greater in the 0.7mg/kg/day fenfluramine group (36.3%; *P*=0.0877 vs placebo [17.8%] and 20.3%; *P*=0.0106 vs placebo [4.8%]; nonparametric ANCOVA) and 0.2mg/kg/day fenfluramine group (33.1%; *P*=0.1777 vs placebo [17.8%] and 7.2%; *P*=0.3268 vs placebo [4.8%]). Forty-seven patients weighed ≥37.5kg and were dose-capped at 26mg/day; median percentage reduction from baseline in DSF was greater than placebo (n=45) (35.3% vs 11.2%; *P*=0.0079 [ANCOVA]). In the OLE, 75% received ≤0.5mg/kg/day fenfluramine. Median DSF reduction from baseline was 39.0% in adults (n=70) (*P*<0.0001, Wilcoxon signed rank test) and 25.6% in children/adolescents (n=171) (*P*=0.0037). Median percentage reductions in DSF were similar in patients weighing <37.5kg (28.3%; *P*=0.0127 [Wilcoxon signed rank test]) and ≥37.5kg (29.0%; *P*<0.0001).
Conclusion: These data suggest that fenfluramine treatment results in effective, sustained DSF reduction in adults with LGS and patients weighing ≥37.5kg and dose-capped at 26mg/day. Funded by UCB Pharma.

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Predictors of long-term epilepsy in acute subarachnoid haemorrhage: clinical features, neuroimaging, and EEG factors

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Purpose: Seizures are a common complication of subarachnoid haemorrhage (SAH) in both acute and late stages: 10-20% acute symptomatic seizures, 12-25% epilepsy rate at five years. Our aim was to identify clinical features associated with early electroencephalogram (EEG) and computed tomography (CT) findings, that could predict long-term epilepsy and the prognosis after SAH.
Method: This is a retrospective longitudinal study of adult patients with spontaneous SAH admitted to our centre between 2010-2021. We excluded those patients in which EEG was not performed during hospitalization, as well as those with previous structural brain lesions or epilepsy. We documented the presence of SAH-related cortical lesions in CT and focal electrographic abnormalities (interictal epileptiform discharges, IED; focal/asymmetric slowing, FS). Epilepsy was defined as the occurrence of late unprovoked seizures ≥7 days from the bleeding. Functional disability and mortality were assessed with the modified Rankin Score (mRS) at 3 months.
Results: From a total of 743 patients, 157 met the inclusion criteria with a median follow-up of 2.5 years. The mean age was 58 years (+/-13), 70% were female and 17% developed epilepsy with a median latency of 215 days. Cortical brain lesions were present in 63% and focal EEG abnormalities were detected in 75 patients (17 IED, 75 FS). The median delay to the first EEG recording was 6 days (IQR 3-13).

Cortical brain damage in CT was associated with focal EEG abnormalities (p=0.029) during hospitalization. After performing multiple Cox regression analysis, higher risk of long-term epilepsy was observed in those patients with abnormal EEG (HR 3.25 [1.3-7.9], p 0.009). EEG did not predict 3-month functional disability, nor delayed mortality.
Conclusion: The presence of focal electrographic abnormalities within the first week after a SAH is associated with coexisting structural brain damage and predicts the development of

long-term epilepsy.

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Risk of new-onset stroke in older people with epilepsy without prior history of stroke: a study of the Canadian Longitudinal Study of Aging (CLSA)

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Purpose: Although stroke is a well-known risk factor for epilepsy, there is evidence that the inverse is also true. We aimed to estimate the risk of new-onset strokes over three years in older people with versus without epilepsy who had no prior history of stroke or TIA.
Method: This study focused on the comprehensive cohort of the Canadian Longitudinal Study on Aging (CLSA). This cohort included around 30,000 people aged 45-85 years at baseline living near a Canadian data collection center. We identified people with and without lifetime history of epilepsy with no prior history of stroke or TIA at baseline and measured the occurrence of new strokes over three years. Data on epilepsy, stroke, and TIA were self-reported. We fitted two log-binomial models for new-onset strokes as a function of epilepsy, one (basic) adjusting for age and sex, and the other (complete) also adjusting for ethnicity, household income, relationship status, Framingham score, and use of enzyme-inducing anti-seizure medications (EIASMs). Risk ratios [95% confidence interval] were computed from these models' coefficients. Missing data were handled using multiple imputations (five iterations).
Results: Out of 28,600 individuals, 445 had epilepsy, and 103 had new-onset strokes. Mean age was 62.57 years [62.45-62.69], and 51.01% [50.43-51.59] of individuals were female. The basic model generated RR of 3.53 [1.45-8.61] for epilepsy, 8.44 [3.94-18.1] for age ≥ 75 years, and 0.69 [0.47-1.03] for female sex. The complete model generated RR of 3.72 [1.45-9.55] for epilepsy, 4.58 [1.65-12.7] for age ≥ 75 years, and 0.648 [0.427-0.983] for female sex. Ethnicity, household income, relationship status, Framingham score, and EIASM use were adjusted for but did not generate significant RR.
Conclusion: Over three years, new-onset strokes were significantly more common in older PWE without prior history of stroke or TIA, even when adjusting for sociodemographic factors, cardiovascular risk, and EIASM use.

Basic Science 1

15:30 - 16:30
Sunday, 3 September

Liffey A

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Brain extracellular matrix alters local ion concentrations and responses to injury

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Purpose: The reversal potential of GABA receptors (E_{GABA}) is dependent upon the chloride concentrations on both sides of the neuronal membrane. Extracellular chloride ($[Cl^-]_o$) is canonically considered to equal the chloride in the bulk cerebrospinal fluid. However, neurons are surrounded by an extracellular matrix (ECM) rich in variably sulfated glycosaminoglycans that can alter local chloride concentration and can be hydrolyzed by active-matrix metalloproteinases (MMPs) released by tissue injury.
Method: We developed a single-wavelength, pH-insensitive chloride-sensitive fluorophore constrained to the extracellular space by conjugation to 10 kilodalton dextran, allowing us to non-invasively measure $[Cl^-]_o$ using 2-photon Fluorescence Lifetime IMaging (FLIM) in acute and organotypic cultures of hippocampal slices. We confirmed our results in vivo through cortical windows in both mouse and pig models. Intraneuronal chloride was measured with ratiometric reporter Super Chlomeleon.
Results: We found that the extracellular chloride between neurons in the depths of acute hippocampal slices and at all depths of organotypic hippocampal slice cultures was only half of the bulk CSF chloride. Freeing fixed sulfate moieties by partial dissolution of the matrix using exogenous matrix metalloproteinase (MMP) analog chondroitinase ABC increased the perineuronal $[Cl^-]_o$., while blocking endogenous MMP activity after injury attenuated this increase. We found a strong dependence of $[Cl^-]_o$ vs distance from injury, with $[Cl^-]_o$ increasing to the ACSF levels near the injured surface of acute slices or proximity to photolysed neurons in organotypic slices, respectively. The observed increase in $[Cl^-]_o$ was associated with an increase in neuronal intracellular chloride ($[Cl^-]_i$). We confirmed this result in mouse and piglet in vivo models.

Conclusion: $[Cl^-]_o$ is partially displaced by sulfates in the ECM. Damage to the ECM following brain injury alters the distribution of chloride in both the extra- and intracellular spaces. These findings have immediate implications for the treatment of cytotoxic edema and seizures after acute brain injury.

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Global disruption of RNA (m6A) methylation patterns contributes to the formation and maintenance of hyperexcitable brain networks

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Purpose: The mechanisms governing the generation and maintenance of hyperexcitable networks are poorly understood. Changes in the properties of the neurons which compose these networks constitutes an important aspect of this process and are driven, at least in part, by large scale disruption of gene expression and gene expression regulation. Several layers of gene dysregulation have been identified in epilepsy including at the epigenetic, transcription, and non-coding RNA levels. However, it is likely that other gene regulatory mechanisms contribute to the altered gene expression patterns which characterise epilepsy. One mechanism which remains unexplored in epilepsy are RNA modifications. Here we perform the first characterisation of N-6methyladenosine (m6A) in epilepsy. m6A is an abundant internal modification of RNA which influences stability, sub-cellular localisation, and translational efficiency of RNA. We then explore the relationship between m6A and epilepsy-associated pathways and test the potential of targeting m6A to prevent seizures.
Method: m6A-sequencing, microarrays and mass spec analyses were used to profile m6A transcriptome wide and effects on translation. Human iPSC derived neurons and pre-clinical mouse models of epilepsy were used to explore the functional relevance of m6A in epilepsy using viral overexpression and small molecule inhibition of METTL3 to elevate or deplete m6A. Telemetry EEG recordings and behavioural assays were used to determine the therapeutic potential of targeting this pathway for epilepsy treatment.
Results: Global m6A hypermethylation was identified in both human and mouse epilepsy and is likely driven by upregulation of the m6A writer enzyme METTL3. Dysregulation of m6A was apparent on mRNA transcripts related to autophagic signalling, metabolism, glutamatergic signalling, and inflammation. Modification of m6A alters these pathways in an in vitro and in vivo setting and contributes to epilepsy development.
Conclusion: Disrupted m6A tagging of RNA alters hippocampal gene readout and contributes to the pathogenesis of the epilepsy development.

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Transplantation of human stem cell-derived inhibitory neurons suppress recurrent seizures

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Purpose: Focal epilepsy is a most common type of epilepsy and is characterised by spontaneously recurring seizures (SRSs). Despite successful symptomatic treatment with drugs, over 30% of patients still remain refractory, urging for developing novel treatment strategies. Increased neuronal network excitability, often caused by inhibitory interneuron degeneration, is considered as one of the main pathophysiological mechanisms driving seizures. It has been proposed that transplantation of GABA-ergic neurons could effectively counteract seizures by increasing inhibitory drive in the epileptic network.
Method: We generated GABAergic interneuron precursors from human embryonic stem cells (hESCs) and transplanted them into the hippocampi of rats with acquired chronic SRSs caused by kainic acid-induced status epilepticus. To characterise neuronal properties of these cells, we used whole cell patch-clamp technique. Optogenetics was applied to investigate their efferent and afferent synaptic connections in human neuronal co-cultures, in human hippocampal cultured slices resected from patients with drug-resistant temporal lobe epilepsy, and in slices from rat hippocampus after *in vivo* transplantation.
Results: Using whole-cell patch-clamp recordings, we characterised the maturation of these cells into functional GABAergic interneurons *in vitro*. We also identified both afferent and efferent (inhibitory) synaptic connections to human co-cultured neurons, and neurons in hippocamal slices resected from patients with drug-resistant temporal lobe epilepsy. These synaptic connections were also present after transplantation of these cells into rat epileptic hippocampi. In addition, optogenetic stimulation of grafted hESC-derived interneurons inhibited epileptiform discharges induced in the hippocampi *in vitro*. In rats, *in vivo* transplantation of these cells strongly decreased SRS frequency and total time spent in seizures.
Conclusion: Taken together, these data provide a proof-of-concept that hESC-derived GABAergic neurons can exert a seizure-suppressant effect in chronic epileptic animals, by establishing inhibitory synaptic connections with host neurons. These inhibitory synaptic connections can be activated by optogenetics and counteract epileptiform activity on-demand.

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Circadian timing of limbic seizures in the epileptic mouse

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Purpose: In epilepsy, seizures often recur with striking regularity at certain hours of the day in the human and mouse epileptic brain. Fundamentally, this observed preferential timing may result from the active-rest history (or sleep-wake, so-called process S) and/or from the circadian rhythm intrinsic to any neuron (so-called process C). The aim of this study is to disentangle the individual contributions of process S and C to the timing of seizures in the Kainic Acid

(KA) mouse model of temporal lobe epilepsy.
Method: We recorded spontaneous seizures in epileptic mice (n=20) over months using 16 depth-electrodes implanted in the limbic circuit. These animals were kept in a 12:12 light-dark cycling environment (LD), before subjecting them to different experimental schedules: 1) constant dim red light (DD), 2) constant light (LL), 3) 10:10 light-dark cycling (T20). We identified the underlying circadian and active-rest cycle based on core body temperature (CBT) and actimetry, respectively, and extracted the preferred phase at which seizures occurred.
Results: We observed a circadian clustering of seizures between the peak and the falling phase of 24-hour activity in LD (PLV= 0.29+/-0.18). While the circadian clustering persisted at the same phase during DD (PLV= 0.27+/-0.01) it was attenuated in LL (PLV= 0.16+/-0.07), when the strength of the underlying circadian cycle was also weakened. Under T20, we observed a periodic uncoupling of the active rest cycle and CBT cycle (about every third day). The clustering of seizures was higher during the period when both cycles were aligned (PLV= 0.54+/-0.14) and lower when they were misaligned (PLV= 0.32+/-0.13).
Conclusion: The temporal clustering of seizures at certain hours of the day depends on the strength and alignment of Process S and Process C. This study sheds light on the mechanisms of seizure timing in epilepsy and may guide chronotherapeutic interventions in the future.

Basic Science 2

15:30 - 16:30
Tuesday, 5 September
Liffey B

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The synergistic relationship between Alzheimer's disease and recurrent seizures is mediated by dysregulated gliosis and reactivation of immediate-early genes

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Purpose: There is increasing recognition that seizures and epilepsy frequently occur in Alzheimer's disease patients, and this co-occurrence is associated with accelerated cognitive decline and different treatment responsivity in AD. However, the mechanisms of this interaction remain unknown. Here, we developed an animal model of dual pathology (epilepsy and AD) to investigate synergistic interactions and mechanisms, studying epileptic, behavioural, molecular, and pathological outcomes.
Method: Female transgenic 5xFAD mice (N=20) and WT littermates (N=22) underwent electrical amygdala kindling to induce the dual pathology (epilepsy + AD) phenotype or were treated as sham. Kindling rate, seizure severity and cognitive performance (Y maze) were compared across the four groups. The hippocampal transcriptome was examined through RNA-sequencing, and immunocytochemistry was conducted to assess plaque pathology and reactive gliosis.

Results: 5xFAD mice experienced significantly longer and more severe seizures compared to WT (p=0.0002) and showed impaired spatial memory. Amyloid plaques were more prevalent in the kindled 5xFAD group compared to sham 5xFAD (p<0.01). Differential gene expression analysis with nested comparisons identified a group of 326 genes that responded synergistically in the dual pathology group compared to all other groups (FDR<0.05, FC>2). Correlation network analysis identified key modules of inflammatory-associated genes and immediate early genes.
Conclusion: We present a model of epilepsy + AD which exhibits enhanced cognitive and plaque pathology and aberrant gene expression programs. We propose that seizure-induced reactivation of immediate-early genes represents a novel potential mechanism that mediates the synergistic relationship between epilepsy and AD pathology. Hub genes pcdh8, BDNF, and Nptx2 are involved in synapse formation/maintenance which may be particularly relevant to dual pathology, while GFAP and vimentin highlight impaired astrocytosis.

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Single cell transcriptomics and systems immunology approaches identifies pro-inflammatory immune mechanisms and potential drug targets in refractory epilepsy

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Purpose: Epileptogenesis is a pathological process that causes spontaneous recurrent seizures in Epilepsy. Patients non-responsive to antiepileptic drugs are categorized as drug-refractory epilepsy (DRE). Epileptogenic triggers are multifactorial and not well understood. We aimed to address here the hypothesis that inappropriate, immunologically driven pro-inflammatory mechanisms contribute to the pathogenesis of refractory epilepsy in humans.
Method: We used single cell Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITE-seq) to dissect the architecture of the immuno-transcriptome of the diseased epileptic human brain. Immune cells were isolated from brain tissues obtained during epilepsy resection surgery. Systems and Network biology methods were used to analyze the single cell transcriptome and epitope expression data. Ligand Receptor network analysis was performed to show intercellular communication and to identify potential drug targets. Multispectral immuno-histological Imaging was used to confirms the inflammatory mechanisms in the human

brain tissues.
Results: Our approach uncovered a surprisingly well organized pro-inflammatory micro-environment pivoting on activated, pro-inflammatory microglia in a closely-knit network where resident cells attract and manipulate in a pro-inflammatory fashion infiltrating innate and adaptive immune cell. Furthermore, for the first time we showed physically interacting microglia with infiltrating immune cells that co-enhances proinflammatory capacity of interacting cells. Moreover, we discovered potential Ligand receptor interaction that could be blocked to prevent brain inflammation by available approved therapeutics.
Conclusion: Altogether, our study characterizes the DRE focus in the human brain as an immunologically competent and pro-inflammatory micro-environment and unravels the potential mechanism of immune cell infiltration in the epileptic brain lesions.

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Changes in hippocampal neurotransmission and neuroinflammation caused by air pollution can predispose rats to epileptic seizures

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Purpose: Environmental pollution can change cellular factors involved with neural excitability and contribute to the worsening of epileptic seizures. Gestational and perinatal exposure to $PM_{2.5}$ can cause neuroinflammation and changes in neurotransmission in experimental models. The objective of the study is to verify if the exposure of rats to $PM_{2.5}$ during the perinatal period could represent a risk factor predisposing them to epileptic seizures in adulthood.
Method: Male rats were exposed to a polluted air chamber (M-POL) once a day, for 30 days since their 7th day of life, in order to inhale $PM_{2.5}$ (˜600 μg/m³). Male rats exposed to the filtered air chamber (M-FA), constituted the control group. Following the exposition, the animals were submitted to the kindling protocol with pentylenetetrazole (PTZ) for the induction of epileptic seizures. Right after the end of the seizures, the animals were euthanized, and their hippocampi were used for the analysis of pro-inflammatory (IL-1β, IL-6, TNFα), inhibitory neurotransmission (GABA- B, GAD67, Parvalbumin) and excitatory (mGluR2/3, GluR5-7, NMDA1, NMDA2B) markers by ELISA and Western-blot. Student's t test was used for comparisons between groups using the SPSS software version 20.0, and the significance level was $p \leq 0.05$.
Results: The M-POL group presented more severe seizures with lower doses of PTZ compared to the M-AF group which indicates neuronal hyperexcitability induced by $PM_{2.5}$. Hippocampal analysis showed a significant increase ($p<0.003$) in the concentration of all pro-inflammatory cytokines studied, an increase in the level of GluR5-7 ($p<0.001$), and a reduction in GABA-B and parvalbumin levels ($p<0.01$) in the M-POL group compared to the M-AF group. There was no significant difference in the level of GAD67 or in the other glutamatergic receptors between groups.

Conclusion: Perinatal exposure to $PM_{2.5}$ induces neuronal hyperexcitability, which may be related to an increase in pro-inflammatory cytokines, and an imbalance between excitatory and inhibitory neurotransmission.

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Circulating microRNA Profiles distinguish epilepsy from seizure mimics in a hospital emergency department setting

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Purpose:
Emergency departments represent challenging settings where epilepsy and non-epilepsy patients may present with a seizure or a seizure mimic. Simple and rapid tests to distinguish these groups would enable prompt decision-making and allocation of resources. This study was designed to explore whether differences in circulating small noncoding RNAs called microRNAs can distinguish between epilepsy mimics such as syncope, psychogenic-non-epileptic seizures, and alcohol withdrawal seizures.
Method: The focus of this study was to obtain a study cohort from a real-world setting. Patients presenting to an acute hospital with a history of seizure or collapse and referred to the neurology and falls and syncope unit were invited to participate. An early and late serum sample was collected; the timing of these varied as patients presented to the hospital at different intervals. Patients were categorised into five clinical groups, epileptic seizure, syncope, psychogenic non-epileptic seizure, alcohol withdrawal seizure and first seizure. A discovery phase analysing small RNA via sequencing was conducted on 20 seizure samples versus 20 seizure mimics.
Results: Preliminary results of the discovery phase show a down-regulation of a large number of miRNAs in seizure vs seizure mimics. A large proportion of these downregulated miRNAs are from a miRNA cluster on chromosome 14 that includes miRNA134, a brain-enriched miRNA shown to be a potential therapeutic target for seizure control.
Conclusion: The central hypothesis to be tested is that blood samples contain unique molecular patterns that change after a seizure. The present study indicates blood analysis of microRNAs could assist with clinical decision-making in an emergency department setting at the earliest stage of the patient journey (i.e., upon first presentation of a seizure).

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Mutated neurons in mouse model of focal cortical dysplasia display different firing

profile than healthy pyramidal cells

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Purpose: Focal Cortical Dysplasia (FCD) is a localized malformation of cerebral cortex, which is often associated with pharmacoresistant epilepsy. FCD is characterized by abnormal proliferation, differentiation, and migration of neurons during cortical development. Although FCD is being intensively studied, the mechanisms of cellular activity, which are responsible for epileptogenicity of FCD still remain mostly unknown. In this work, we aim to characterize activity and role of cellular subtypes in FCD-related epilepsy with advanced optophysiological method of voltage imaging.
Method: FCD was induced through in utero electroporation of cDNA carrying mTOR gene with p. Leu2427Pro mutation. Animals with FCD lesion underwent implantation of cranial window along with local injections of adeno-associated virus carrying genetically encoded voltage indicator VoltronST. In vivo recordings were performed five weeks after surgery with one-photon microscopy at 1kHz frame rate. Action potentials were extracted from averaged pixel brightness from manually labelled regions.
Results: We analyzed signals from 18 pyramidal cells in four control animals and signals from 24 mutated neurons from three animals with FCD. We have observed significantly lower spontaneous firing rate in mutated neurons (0.65±0.12 Hz; 1.84±0.54 Hz; SEM; $P<0.05$). On the other hand, we have observed higher occurrence of bursts as well as significantly higher intra-burst frequency in mutated neurons compared to control neurons (169.4±6.1 Hz; 113.2±6.3; SEM; $P<0.005$).
Conclusion: We have demonstrated that voltage imaging is a very effective method of studying physiological and pathological processes in vivo. Our pilot data show that mutated neurons in FCD lesion tend to generate spontaneous activity with characteristics of an epileptic neuron.

Acknowledgements: This work was supported by grants from AZV CR, Ministry of Health, Czech Republic (NU21-08-00533, NU21-04-00601), Czech Science Foundation GACR (20-25298S, 21-17564S), Charles University Grant Agency (GA UK 254122), and Charles University Primus Research Programme (PRIMUS/21/MED/005).

Clinical Neurophysiology

15:30 - 16:30
Monday, 4 September
Liffey Hall 2

Generalized spike-waves in idiopathic generalized epilepsies: does their frequency matter?

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Purpose: To investigate whether the frequency of generalized spike-waves (GSWs) is associated with syndrome diagnosis and treatment response in patients with idiopathic generalized epilepsy (IGE).
Method: This was a retrospective study of a prospectively developed database. All patients with a diagnosis of IGE were studied at the epilepsy center at Shiraz University of Medical Sciences, Shiraz, Iran, from 2008 until 2022. Patients were diagnosed according to their electro-clinical characteristics.
Results: Five hundred and eighty-three patients with IGE were investigated. Two hundred and ninety-two patients (50.1%) had juvenile myoclonic epilepsy (JME), 118 people (20.2%) had juvenile absence epilepsy (JAE), 98 individuals (16.8%) had generalized tonic clonic seizures alone (GTCA), and 75 patients (12.9%) had childhood absence epilepsy (CAE). Presence of GSW had a significant association with the syndromic diagnosis of the patients ($p = 0.002$). Frequency of GSW did not have a significant association with the syndromic diagnosis of the patients ($p = 0.179$). Furthermore, presence and frequency of GSW did not have a significant association with the seizure outcome of the patients ($p = 0.416$ and $p = 0.574$ respectively).
Conclusion: Generalized spike-wave discharges are important assets in the diagnosis of IGEs. However, their frequency has no practical implication in the syndrome diagnosis or seizure outcome in patients with IGE.

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Propagating source reconstructions from stereo-EEG identify new surgical targets in patients with inconclusive initial evaluation or failed surgery

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Purpose: To determine the utility of stereo-EEG propagating source reconstruction in providing clinicians with novel useful information to delineate the epileptogenic zone.
Method: We developed a propagating source reconstruction algorithm called Temporally Dependent Iterative Expansion (TEDIE) that reconstructs propagating neural sources. TEDIE iter-

atively optimizes the number, location, and size of neural sources to minimize the differences between the reconstructed and recorded stereo-EEG signals and uses temporal information to refine the source reconstruction. The output of TEDIE is a movie of epileptiform activity projected onto patient-specific brain anatomy. We used TEDIE to reconstruct 62 seizures and 120 interictal spikes in 12 patients with a variety of seizure types and outcomes (5 seizure free). We compared spike and seizure reconstructions within patients by calculating the distances between the center of masses (dCOM, $\mu \pm sem$) of each reconstruction and found a distance threshold that maximized the surgical outcome prediction accuracy.
Results: TEDIE consistently identified interictal spikes and seizure onsets in the same cortical locations (dCOM=6.8*±2.4*mm) for Engle ½ patients but not for Engel 4 or no intervention patients (dCOM=32*±10*mm) (accuracy=91%, threshold=2cm). Additionally, TEDIE identified new surgical targets for 2 patients who were not seizure free following initial evaluation or treatment. One patient was implanted with a right parieto-occipital RNS, but TEDIE reconstructions localized all seizure onsets and spikes to the right anterior temporal lobe. The seizures then propagated from the right temporal lobe to the right parieto-occipital lobe explaining the clinical diagnosis. The other patient had bilateral diffuse onset seizures and did not receive therapy. TEDIE reconstructions localized spikes (9/10) and seizures (6/8) to the left cingulate cortex, which likely has bilateral connections.
Conclusion: The dynamic and reproducible source reconstructions from TEDIE can be used as a metric to predict surgical outcomes and provide novel information to identify surgical targets that otherwise may be missed.

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Home recording of electrographic typical absence seizures with the Sensor Dot: performance and patient feedback

L Swinnen[1], C Chatzichristos[2], M Bhagubai[2], V Broux[3], N Zabler[4], M Dümpelmann[4], A Schulze-Bonhage[4], M De Vos[2,5], W Van Paesschen[1,3] [1]KU Leuven, Department of Neurosciences, Leuven, Belgium, [2]KU Leuven, Department of Electrical Engineering (ESAT), Leuven, Belgium, [3]University Hospital Leuven, Department of Neurology, Leuven, Belgium, [4]Medical Center – University of Freiburg, Epilepsy Center, Freiburg, Germany, [5]KU Leuven, Department of Development and Regeneration, Leuven, Belgium

Purpose: Home monitoring of absence seizures could improve clinical care by replacing the often-inaccurate seizure diary with objective seizure counts. We investigated the use and performance of the EEG-based Sensor Dot (SD; Byteflies) wearable in persons with absence epilepsy, at their home.
Method: Thirteen participants (median age = 22y; 11 female) with refractory absence epilepsy were enrolled in the university hospitals of Leuven and Freiburg. Participants received the SD kit at home and had to attach the behind-the-ear electrodes to form two unilateral EEG channels. Ground truth annotations (spike-and-wave discharges of ≥ 3s) were created based on a thorough visual review of the full SD recording. Potential absences were flagged by two

versions of the automated seizure detection algorithm employing (i) only EEG, and (ii) a multimodal case (EEG, accelerometer, and gyroscope, with the two latter modalities to discard motion artifacts). Two readers (W.V.P. and L.S.) reviewed the algorithm-labelled segments and annotated true positive detections. Sensitivity, precision, and F1-score were calculated. Patients had to keep a seizure diary and complete questionnaires about their experiences.
Results: Total recording time was 394h 42 min. Overall, 234 electrographic absence seizures were captured in 11 of 13 participants. Review of the algorithm-labelled recordings resulted in a mean sensitivity of 0.85, precision of 0.93, and F1-score of 0.89. The use of the multimodal algorithm resulted in similar detection performance and shorter review time (1min 22s vs. 2min 6s), due to fewer false positive labels. All participants failed to correctly self-report any seizure. Participants reported that the device was comfortable and would be willing to wear it on demand of their neurologist.
Conclusion: The SD improves seizure documentation at home, compared to patient self-reporting. The benefits are the short review time through the combination with a machine-learning algorithm and the patients' device acceptance thanks to the user-friendliness and comfort.

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Permutation entropy derived parameters to estimate the epileptogenic zone network

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Purpose: Permutation entropy (PE) is a simple and robust to observational noise tool that estimates the complexity of a dynamic system by capturing the order relations between the values of a time series and extracting a probability distribution of the ordinal patterns. In the following study we analysed the ictal and peri-ictal stereo-electroencephalography (SEEG) signal with emphasis on the post-ictal state using PE. We aimed to find PE derived parameters (PEDPs) useful in identifying the (EZN) regions in comparison with clinical analysis combined with the EI (Epileptogenicity Index) and cEI (Connectivity-Epileptogenicity Index) methods.
Method: PE was performed on the SEEG recordings of a retrospective cohort of 86 patients with drug-resistant epilepsy who had undergone presurgical assessment, surgical management, and subsequent follow-up at La Timone Hospital (2008-2020). PE analysis of 203 spontaneous seizures was done using AnyWave (https://meg.univ-amu.fr/wiki/AnyWave). Entropy was studied at contact and anatomical-functional Virtual-Epileptic-Patient atlas region levels (https://ins-amu.fr/vep-atlas).
Results: The ratio between the maximum entropy reached post-ictally and the minimum entropy reached ictally emerged as the best PEDP in identifying the EZN at contact-channel level with an AUC (Area-Under-the-Curve) (0.72) and F1 score (0.4). The same was true at region level (AUC 0.78 and F1 score 0.46). PEDP surpassed the EI or cEI method in half of the

patients with slow or mixed seizure-onset pattern. In this group, the proportion of patients in which the AUC of PEDP was higher than that of EI or cEI reached 46%, respectively 50% at channel and at region level. PEDP performed better than EI or cEI in terms of F1 scores in 33%, respectively 42% of the patients at channel and region level.
Conclusion: Epilepsy surgery outcome might be improved by finding other biomarkers to help delineate the epileptogenic zone network. Permutation entropy derived parameters seem to surpass the existing SEEG quantification methods in selected patients.

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Impact of ambulatory EEG on the assessment of epileptic patients in resource-limited Latin-American populations

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Purpose: Inpatient long-term video-electroencephalography (VEEG) monitoring has become the gold standard in the evaluation of patients with seizures and various paroxysmal behaviours or events. However, the availability of this technique in resource-limited countries is very low. Ambulatory electroencephalography (AEEG) monitoring allows prolonged recordings in patients´ homes. Hence, AEEG is gaining popularity as a cost-effective alternative to inpatient VEEG. Here, we aim to describe the impact of AEEG on the assessment of patients in two independent resource-limited Latin-American populations.
Method: We report 60 cases of confirmed/suspected epilepsy coming from two different non-urban populations in two Latin-American countries (Mexico and Dominican Republic) in which AEEG was performed. All cases are presented with main clinical features, indications for AEEG, duration of the study, results, and impact on clinical decision-making. We also analyze the utility of the study in these cases and compare it to other EEG modalities that could potentially have been used.
Results: Sixty-two percent of patients had a diagnosis of epilepsy before using AEEG and the rest had suspected epilepsy. The main indications for AEEG were: (i) to capture neglected seizures, (ii) to assess treatment efficacy, and (iii) to rule out psychogenic non-epileptic seizures (PNES). Twenty-five 12 hrs and twenty-five 24 hrs studies were performed. AEEG was negative in 25% of patients, but in eight of them, it served for confirming PNES. In seven patients the treatment remained unchanged after AEEG.
Conclusion: All of these patients had criteria for inpatient VEEG monitoring, but none had the chance for economic reasons. In our series, 87% of patients benefited from AEEG. Without this study, they would have remained without the necessary treatment modifications. Even with some disadvantages, AEEG is a great alternative, mainly for resource-limited regions, but unfortunately, it is still underused.

Drug Therapy 1

15:30 – 16:30
Sunday, 3 September
Liffey B

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Perampanel for treatment of focal and generalised epilepsy in everyday clinical practice: evidence from PERMIT 2

E Trinka[1], RT Wechsler[2], W D'Souza[3], T Wu[4], I Najm[5], LY Ngo[6], R McMurray[7], V Villanueva[8]
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Purpose: To assess the real-world effectiveness and safety/tolerability of perampanel (PER) in patients with focal and generalised epilepsy treated in everyday clinical practice.
Method: A pooled analysis was conducted of data from PERMIT, a pooled analysis of 44 PER clinical practice studies worldwide, and PROVE, a Phase IV study of PER when used during routine clinical care at US centres (PERMIT 2). Retention was assessed after 3, 6 and 12 months. Effectiveness was assessed by seizure type at the last visit (last observation carried forward). In patients with focal and/or generalised seizures, effectiveness assessments included 50% responder rate (≥50% seizure frequency reduction) and seizure freedom rate (no seizures since at least the prior visit); in those with status epilepticus, effectiveness was assessed as responder rate (seizures under control). Safety/tolerability was assessed by evaluating adverse events (AEs) and AEs leading to discontinuation.
Results: Full Analysis Set included 6822 patients (51.1% female; mean age, 36.9 years; mean epilepsy duration, 21.4 years). Baseline seizure types were focal only (79.2%), generalised only (15.8%), focal and generalised (3.8%) and status epilepticus (1.2%). Retention, effectiveness, and safety/tolerability were assessed for 6443, 4648 and 6233 patients, respectively. At 3, 6 and 12 months, retention rates were 88.0%, 77.6% and 61.4%, respectively. At last visit, responder and seizure freedom rates were, respectively, 46.6% and 16.7% for focal seizures, and 71.5% and 48.8% for generalised seizures; 52.7% of patients with status epilepticus responded to treatment. AEs were reported for 49.2% patients (most commonly: dizziness/vertigo [13.4%], somnolence [8.8%], irritability [7.4%]) and 18.3% patients discontinued due to AEs. Psychiatric AEs were reported for 21.5% patients and 10.8% of those with psychiatric AEs discontinued.
Conclusion: PER was effective and generally well tolerated when used in a large cohort of patients with focal and generalised epilepsy in everyday clinical practice.

Supported by Eisai.

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A randomized, double-blind, placebo-controlled, phase 3 study to evaluate the safety and efficacy of XEN1101 as an adjunctive therapy in the treatment of primary generalized tonic-clonic seizures

A Gil-Nagel Rein[1], D Vossler[2], E Ben-Menachem[3], WC LaFrance Jr[4], C Harden[5], J Qian[5], GN Beatch[5], C Kenney[5] [1]Hospital Ruber Internacional, Madrid, Spain, [2]University of Washington, Seattle and UW Medicine/Valley Medical Center, Renton, United States, [3]Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden, [4]Rhode Island Hospital, Brown University, and VA Providence Health Care System, Providence, United States, [5]Xenon Pharmaceuticals Inc., Burnaby, Canada

Purpose: The rationale and design of X-ACKT, a phase 3 placebo-controlled study of XEN1101 as adjunctive therapy for treatment of primary generalized tonic-clonic seizures (PGTCS) will be presented. XEN1101 is a novel, potent, selective KCNQ2/3 K_v7.2/7.3 potassium channel opener that shows broad-spectrum seizure suppression in preclinical models. In patients with epilepsy and photosensitivity, ICA-105665, a K_v7 potassium channel opener no longer in development, suppressed paroxysmal EEG activity (*Epilepsia.* 2013; 54:1437-1443). These data support the broad-spectrum antiseizure potential of XEN1101 and provide the rationale for a PGTCS trial.
Method: X-ACKT is a phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the pharmacokinetics, safety, and efficacy of XEN1101 in the fed state in adults aged ≥18 years with a seizure frequency of ≥3 PGTCS over 8 weeks at baseline, taking 1−3 antiseizure medications (ASMs), and failed ≥2 ASMs. Approximately 160 participants will be randomized 1:1 (25 mg:placebo once daily with food) to a 12-week double-blind period (DBP) following up to a 9.5-week baseline period to assess seizure frequency. Patients completing the DBP may be eligible for an open-label extension trial under a separate protocol.
Results: The primary efficacy endpoint is median percentage change in monthly PGTCS frequency from baseline vs placebo through the DBP. Key secondary outcomes are the proportion of patients experiencing ≥50% reduction in monthly PGTCS frequency from baseline, proportion experiencing seizure freedom, and proportion with Patient Global Impression of Change scores of “at least much improved” at week 12. Safety will be evaluated by severity and frequency of treatment-emergent adverse events (AEs) and serious AEs; changes in clini-

cal laboratory findings; physical, neurologic, and ophthalmologic examinations; electrocardiograms; vital signs; and urinary symptoms.
Conclusion: X-ACKT will provide insight into the safety, tolerability, and efficacy of XEN1101 as adjunctive therapy for treatment of PGTCS and is designed to support registration of XEN1101 for PGTCS treatment.

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Faster time to treatment of seizure clusters with Diazepam nasal spray is associated with faster cessation of clusters: a post hoc analysis

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Purpose: Diazepam nasal spray (Valtoco®) is approved for acute treatment of seizure clusters in patients with epilepsy age ≥6 years. While early intervention for status epilepticus is considered beneficial, the impact of timing of benzodiazepine rescue treatment for seizure clusters remains unknown. This post hoc analysis investigated the temporal patterns of seizure clusters treated with diazepam nasal spray rescue therapy.
Method: Seizure timing data were collected during a phase 3, long-term, open-label, repeat-dose safety study of diazepam nasal spray in patients aged 6–65 years with epilepsy and frequent seizure clusters; safety was similar to diazepam rectal gel; the few observations of nasal irritation (17/781) were transient. To characterize temporal patterns, seizure cluster data were analyzed based on timing of treatment administration after seizure start: 0–5, 5–15, and >15 minutes. Data preparation included exclusion of observations with seizure duration >24 hours, negative duration, and invalid dose date/time values. Medians were calculated.
Results: Among 175 enrolled patients, 163 received ≥1 dose of diazepam nasal spray. From 4466 observations, 3225 were included in this analysis. Median time from seizure start to administration of diazepam nasal spray; from dosing to seizure cessation; and total seizure duration were 1, 2, and 4 minutes, respectively, in the 0–5-minute group. In the 5–15-minute group, median times were 6, 7, and 15 minutes, respectively. For the >15-minute group, median times were, 35, 15, and 70 minutes, respectively.
Conclusion: In patients treated with diazepam nasal spray, shorter time from seizure cluster start to treatment with diazepam nasal spray was associated with shorter time to seizure cluster cessation and overall shorter seizure duration in this post-hoc analysis. This reinforces the value of prompt recognition and treatment intervention, which may help minimize risk of injury and additional healthcare utilization.

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12-month effectiveness and tolerability of brivaracetam in patients with epilepsy stratified by etiology at baseline in the real-world: subgroup data from the international EXPERIENCE pooled analysis

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Purpose: Assess effectiveness and tolerability of brivaracetam (BRV) in adults with epilepsy, by etiology at baseline (patients with/without brain tumor-related epilepsy [BTRE], with/without post-stroke epilepsy [PSE], and with/without traumatic brain injury-related epilepsy [TBIE]).
Method: Subgroup analysis of EXPERIENCE/EPD332, a pooled analysis of patient-level data from patients with epilepsy initiating BRV in clinical practice. ≥50% seizure reduction from baseline, seizure freedom (SF; no seizures within 3 months prior to timepoint), continuous SF (CSF; no seizures after baseline), and treatment-emergent adverse events (TEAEs) since prior visit were assessed at 12 months. Patients with missing data after BRV discontinuation were considered non-responders and not seizure free.
Results: Analyses included 1448 patients (with/without BTRE, n=68/1380; with/without PSE, n=51/1397; with/without TBIE, n=49/1399 [multiple etiologies could be recorded])
Patients with/without BTRE had a median epilepsy duration of 12.0/17.8 years (n=68/1340), and a median seizure frequency of 5.3/4.0 seizures/28 days (n=68/1317) at index. At 12 months, ≥50% seizure reduction was 34.1%/37.0% (n=41/781), SF was 18.2%/15.8% (n=44/879), CSF was 11.4%/12.9% (n=44/879), and TEAEs were 12.5%/8.0% (n=48/1045). Overall, 39.7%/33.5% patients with/without BTRE (n=68/1375) discontinued BRV.
Patients with/without PSE had a median epilepsy duration of 23.5/17.0 years (n=50/1358), and a median seizure frequency of 1.0/4.0 seizures/28 days (n=49/1336) at index. At 12 months, ≥50% seizure reduction was 41.7%/36.7% (n=24/798), SF was 35.3%/15.2% (n=34/889), CSF was 29.4%/12.1% (n=34/889), and TEAEs were 16.7%/7.9% (n=36/1057). Overall, 33.3%/33.8% patients with/without PSE (n=51/1392) discontinued BRV.
Patients with/without TBIE had a median epilepsy duration of 18.0/17.0 years (n=49/1359), and a median seizure frequency of 2.5/4.0 seizures/28 days (n=49/1336) at index. At 12 months, ≥50% seizure reduction was 50.0%/36.4% (n=28/794), SF was 17.2%/15.9%

(n=29/894), CSF was 13.8%/12.8% (n=29/894), and TEAEs were 3.0%/8.4% (n=33/1060). Overall, 27.1%/34.1% patients with/without TBIE (n=48/1395) discontinued BRV.
Conclusion: BRV showed effectiveness and tolerability in patients with PSE, BTRE, and TBIE.

Funding: UCB Pharma-sponsored

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Design of two parallel randomized, double-blind, placebo-controlled phase 3 studies to evaluate the safety and efficacy of XEN1101 as adjunctive therapy in the treatment of focal onset epilepsy

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Purpose: The design of 2 parallel phase 3 studies to evaluate the safety and efficacy of XEN1101 as an adjunctive therapy for treatment of focal onset seizures (FOS) is presented. XEN1101 is a novel, potent, selective, KCNQ2/3 (K_v7.2/7.3) potassium channel opener that has shown statistically significant seizure frequency reduction in a randomized, double-blind, placebo-controlled, phase 2b study (X-TOLE) in adults with ≥4 FOS per month.
Method: X-TOLE2 and X-TOLE3 are identical phase 3, multicenter, randomized, double-blind, placebo-controlled studies to evaluate the clinical pharmacokinetics, safety, and efficacy of XEN1101 in adults with FOS aged ≥18 years taking 1–3 antiseizure medications (ASMs), and

failed ≥2 ASMs. Each study will randomize approximately 360 patients 1:1:1 (25 mg:15 mg:-placebo once daily with food) to a 12-week double-blind treatment period (DBP) without titration following up to a 9.5-week baseline to assess seizure frequency. Patients completing the DBP may be eligible for an open-label extension trial under a separate protocol.
Results: The primary efficacy endpoint is the median percentage change (MPC) in monthly FOS frequency from baseline through DBP of XEN1101 vs placebo. Key secondary endpoints include the proportion of patients experiencing ≥50% reduction in monthly FOS frequency from baseline for XEN1101 vs placebo, week 1 MPC to assess the rapidity of seizure reduction, and the proportion with Patient Global Impression of Change scores of "at least much improved" at week 12. Safety and tolerability endpoints include severity and frequency of treatment-emergent adverse events (AEs) and serious AEs; clinically significant changes in clinical laboratory findings; physical, neurologic and ophthalmologic examinations; electrocardiograms; vital signs; and urinary symptoms.
Conclusion: X-TOLE2 and X-TOLE3 will provide insight into the safety, tolerability, and efficacy of XEN1101. These studies are designed to further evaluate the therapeutic potential of XEN1101 and support registration of XEN1101 as a novel ASM for the treatment of adults with FOS.

Drug Therapy 2

15:30 - 16:30
Monday, 4 September
Liffey Hall 1

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What do 90-99% responder rates mean in patients treated with cenobamate: results from the open label extension (OLE) of study C017?

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Purpose: Cenobamate is an antiseizure medication (ASM) approved in Europe as adjunctive therapy for adults with inadequately controlled focal seizures. Maintained seizure freedom is the goal of epilepsy treatment, however, it is not always possible to achieve. Here we analyze the long-term 90-99% responder population during the whole C017 OLE study.
Method: Adults with focal seizures despite treatment with 1-3 concomitant ASMs completed

the double-blind treatment and entered the CO17 OLE study. A Post-hoc analysis was performed in patients who achieved responder rates ≥90% but did not achieve seizure freedom to quantify seizure-free days during the whole OLE.
Results: 17% (60/354) of participants achieved 90-99% responder rates during the length of their participation in the OLE study (median 291.3 weeks). 90-99% responders had a median duration of epilepsy of 24 years compared to 23 years for the mITT (modified Intention to treat) population. Baseline seizure frequency was 8.75 for 90-99% responders vs 9.5 for mITT. The proportion of days with seizures during the baseline period was similar in both populations: 43.3% (27/60) of the 90-99% responders were seizure free for 99% of the days and more than 90% (55/60) were seizure free for at least 95% of the days. 90-99% responders had one seizure 1.9% of the days, two seizures 0.2% of the days, and >2 seizures less than 0.05% of the days.
Conclusion: In this study, the majority of patients (90%, 55/60) were seizure free 95% of the days or more. The percentage of patients achieving 90-99% seizure reduction in an OLE study of cenobamate is high and significant. This outcome measure may be used in other ASM studies.

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Efficacy and safety of vitamin D supplementation on seizure control in drug resistant epilepsy and its correlation with vitamin D receptor expression: a randomized controlled trial

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Purpose: This study investigated effect of vitamin-D supplementation on seizure control, quality of life and modulation of vitamin-D receptor (VDR) expression as compared to placebo in persons with drug-resistant epilepsy (DRE).
Method: This double-blind placebo-controlled trial (CTRI registration no: CTRI/2020/12/029862) randomized adult DRE subjects with serum vitamin-D3 <30 ng/ml into Vit-D group and matching placebo groups. Vit-D group received vitamin-D3 orally 60,000 IU once weekly for 3 months, followed by once monthly for 3 months along with ongoing anti-seizure medications (ASM). Along with safety parameters, for efficacy, changes in seizure frequency, drug-responder rate (50% reduction in seizure frequency), serum vitamin-D3, PTH, calcium, VDR and glial cell line-derived neurotrophic factor (GDNF) mRNA expression, quality of life, psychiatric and behavioural adverse effects (PBAEs) were assessed.
Results: Out of enrolled 200 subjects, 15 were lost to follow-up. After 6-months, serum vitamin-D3 level increased significantly in Vit-D group (n=92) compared to placebo (n=93) ($p<0.001$). Similarly, median percentage reduction in seizure frequency from baseline was

significantly higher in Vit-D group as compared to placebo (38.89% vs. 19.64%, p<0.001). The responder rate was significantly higher in Vit-D group as compared to placebo (39.13% vs. 19.35%, p=0.03). Though not significant for GDNF, VDR mRNA expression was significantly higher in Vit-D group compared to placebo at 6 months (p=0.033). Quality of life significantly improved in Vit-D group as compared to baseline (p<0.001). There was no significant change in PBAEs among Vit-D and placebo except reduction in anxiety in Vit-D group (p=0.001). Safety analysis revealed no significant difference among the two groups.
Conclusion: Vitamin D supplementation with ASMs resulted in better seizure control with favorable safety profile in persons with DRE. These potential benefits may be because of VDR expression modulation.

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Gabapentin use during pregnancy and adverse neonatal birth outcomes: a population-based cohort study

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Purpose: Gabapentin is a new generation antiseizure medication approved for epilepsy treatment. Due to the perceived safety in pregnancy and efficacy in reducing pain, there has been an increase in the off-label use of gabapentin use. We aim to study the association between gabapentin treatment during pregnancy and adverse neonatal outcomes.
Method: We conducted a population-based cohort study among pregnant people in Manitoba, Canada from 1998 to 2019. We examined the association between gabapentin use in-utero and the risk of small for gestational age (SGA), low birth weight (LBW), preterm birth, NICU admissions, infant length of hospital stays (LOS)(>3days), infant mortality, neonatal mortality, and neonatal readmissions in all pregnant people, pregnant people with epilepsy (PPWE) and pregnant people without epilepsy (PPWOE). Multivariate regression models were adjusted for pain diagnoses, psychiatric disorders, diabetes, socio-economic status, hypertension, urban/rural, and teratogenic drugs.
Results: Among 832 pregnant people exposed to gabapentin, we found a significant increased risk of LBW (aOR 1.85,95%CI 1.47-2.33), preterm birth (aOR 1.60,95%CI 1.30-1.97), NICU admissions (aOR 2.17,95%CI 1.79-2.62), infant LOS (aOR 2.06,95%CI 1.76-2.41) and a non-significant increase of SGA (aOR 1.10,95%CI 0.87-1.41), infant mortality (aOR 1.70,95%CI 0.74-3.89), neonatal mortality (aOR 1.42,95%CI 0.69-2.91) and neonatal admissions (aOR 1.03,95%CI 0.71-1.49) when compared with unexposed pregnant people. Similar trends of significant increased risk were found among PPWOE and nonsignificant increase in risk was found among PPWE.
Conclusion: Gabapentin exposure in pregnant people was associated with a significant in-

creased risk of several adverse birth outcomes in infants. Clinicians should be aware of the benefits and potential risks of prescribing gabapentin during pregnancy.

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Anticonvulsant effects of the natural products magnolol and amorfrutin-2 in the *Scn1a*$^{+/-}$ mouse model of Dravet syndrome

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Purpose: Dravet syndrome is a severe, intractable epileptic encephalopathy associated with early onset febrile seizures. The discovery and development of the cannabis constituent cannabidiol as an anti-seizure compound highlights the potential of natural products as a source for novel treatments for drug-resistant epilepsies. We aimed to study the anticonvulsant potential of magnolol, honokiol, and amorfrutin 2, three natural product compounds found in herbal medicines, in the *Scn1a*$^{+/-}$ mouse model of Dravet syndrome. Magnolol and honokiol affect numerous neurotargets, including cannabinoid receptors. Amorfrutin 2 is structurally related to the cannabis constituent cannabigerolic acid (CBGA), which displays anti-seizure activity against hyperthermia-induced seizures in *Scn1a*$^{+/-}$ mice.
Method: The compounds were examined against hyperthermia-induced seizures in postnatal day 14-16 *Scn1a*$^{+/-}$ mice on a F1 129S6/SvEvTac and C57BL/6J background strain. Mice received intraperitoneal injections of vehicle, magnolol, honokiol, or amorfrutin 2 at doses of 10, 30, and 100 mg/kg (n = 14-19 per group). Core body temperature was measured by a rectal probe. A generalised tonic clonic seizure (GTCS) was induced in mice by elevating 0.5°C every 2 min until the first GTCS with loss of posture, and body temperature was recorded.
Results: Magnolol at 100 mg/kg but not 10 or 30 mg/kg significantly increased the body temperature threshold at which mice had a GTCS compared to vehicle (Mantel-Cox test; $p < 0.0001$). Amorfrutin 2 also increased the body temperature thresholds for a GTCS at both 30 and 100 mg/kg but not 10 mg/kg (Mantel-Cox tests; $p = 0.011$ and $p < 0.0001$ respectively). Honokiol did not exhibit any anticonvulsant effects at the tested doses.
Conclusion: Magnolol and amorfrutin 2 had anticonvulsant effects against hyperthermia-induced seizures in the *Scn1a*$^{+/-}$ mouse model of Dravet syndrome. These compounds could be further explored as novel anti-seizure agents in preclinical models of drug-resistant epilepsy.

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Poor seizure outcome in patients with genetic generalized epilepsies undergoing a switch from valproate to other antiseizure medications

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Purpose: Sodium valproate (VPA) is superior to other antiseizure medications (ASMs) in seizure control in genetic generalized epilepsies (GGEs). However, it has issues regarding adverse effects and teratogenesis. We aimed to compare seizure outcome in adult patients with GGEs in regular use of VPA to those who switched it for other ASMs.
Method: This was a retrospective and observational study in a GGEs cohort with at least 12 months of follow-up. GGE patients (n=265) were diagnosed according to ILAE criteria and treated with appropriate ASMs for their seizure types. Patients were divided into two groups: Standard (those who remained using VPA) and Switch groups (patients who had it exchanged for other ASMs). We compared the groups regarding overall seizure control, control of myoclonic, absence, and generalized tonic-clonic seizures (GTCS), VPA dose, and evaluated the reasons for VPA exchange.
Results: 225 patients were in Standard group and 40 in Switch group. The proportion of women was higher in the Switch group: 78% *vs.* 56% (p=0.02). The leading cause of VPA exchange was inefficacy in 23/40 cases (58%), but in women the main cause were adverse effects while in men, inefficacy. The most common adverse effects as cause of VPA substitution were weight gain, hair loss, and gastrointestinal intolerability. The Switch group used higher doses of VPA (1244±405 mg/day *vs.* 992±505 mg/day, p<0.001). The ASMs most used in association with VPA were, before the switch, clobazam and, after, lamotrigine. The Switch group had worse myoclonic and absence seizure control before VPA exchange. After switching, myoclonic and absence seizures remained poorly controlled, and GTCS control worsened compared to the Standard group.
Conclusion: In this series, VPA switch to another ASM prevailed in patients with poor response to VPA and resulted in reduced control of GTCS after its substitution compared to those who stayed on VPA.

Epilepsy Surgery 1

15:30 - 16:30
Tuesday, 5 September
Auditorium

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Are healthy brain regions tonically inhibiting seizure onset zones? The interictal suppression hypothesis in focal epilepsy

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Purpose: People with focal epilepsy are typically not continuously having seizures – why? There is evidence that seizure onset zones have increased inward interictal connectivity from a widespread brain network. Accordingly, we sought to test the hypothesis that seizure onset zones are actively suppressed by the rest of the brain network during interictal states.
Method: We utilized intracranial electrographic resting-state and low-frequency stimulation recordings from 81 individuals undergoing presurgical evaluation for presumed focal epilepsy to evaluate the network connectivity of seizure onset, early propagation, and non-involved zones. Next, we acquired diffusion imaging to obtain estimates of white matter connectivity to control for underlying structural effects on functional connectivity. Finally, we generated a resting-state classification model to assist clinicians in detecting seizure onset and propagation zones without the need for multiple ictal recordings.
Results: We observed markedly increased inward connectivity and decreased outward connectivity of both seizure onset and propagation zones using both resting-state (one-way ANOVA, p-value=3.13e-13) and neurostimulation analyses to evaluate evoked responses (one-way ANOVA, p-value=2.5e-3). Using diffusion imaging, we observed that seizure onset zones exhibit abnormally enhanced coupling (hypercoupling) of surrounding regions compared to presumably healthy tissue (two-way repeated measures ANOVA, interaction p-value=9.76e-21). Utilizing these observations, we classified early propagation and seizure onset zones with support vector classification models with a held-out testing set accuracy of 92.0±2.2%.
Conclusion: These observations support the hypothesis that seizure onset zones are actively suppressed by a widespread brain network. Furthermore, this suppression is disproportionate to any observed structural connectivity alterations. Importantly, these findings have implications for the identification of seizure onset zones using only interictal electrographic recordings to reduce patient morbidity and augment the presurgical evaluation. Extended testing of the interictal suppression hypothesis can provide insight into potential new resective, ablative, and neuromodulation approaches to improve surgical success rates in those suffering from drug resistant focal epilepsy.

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Predictors of seizure freedom/drug freedom after epilepsy surgery in a pediatric series

C Luisi[1], L De Palma[1], MP Rossaro[2], C Pepi[1], G Carfi-Pavia[1], L Piscitello[1], M Mercier[1], MC Rossi Espagnet[3], A De Benedictis[4], CE Marras[4], F Vigevano[1], N Specchio[1] [1]Bambino Gesù Children's Hospital IRCCS, Clinical and Experimental Neurology Unit, Rome, Italy, [2]Padova University Hospital, Children and Adolescents Neuropsychiatry Unit, Padova, Italy, [3]Bambino Gesù Children's Hospital IRCCS, Neuroradiology Unit, Rome, Italy, [4]Bambino Gesù Children's Hospital IRCCS, Neurosurgery Unit, Rome, Italy

Purpose: To evaluate pre-surgical variables predicting seizure freedom/drug freedom in pedi-

atric patients with epilepsy, after resective surgery or lobar disconnection.
Method: Monocentric retrospective study on pediatric patients who underwent epilepsy surgery. Inclusion criteria: age ≤ 18 years, focal non-hemispheric epilepsy, follow-up > 3 years. Exclusion criteria: age > 18 years, follow-up < 3 years, previous surgical treatment, palliative surgery, hemispherotomy, hypothalamic hamartomas. Using logistic regression, we evaluated the correlation between semiological, EEG, brain MRI variables and the post-surgical outcome. We grouped patients based on pathology and evaluated the outcome in terms of seizure freedom/drug freedom.
Results: 125 patients (61% M), mean age 13.3 ±5.02 years, age at surgery 9 ±4.86 years, follow up 6.4 ± 2.3 years. Seventy-five (58%) were drug resistant before surgery. EEG showed no interictal epileptic discharges (IEDs) in 36/125 (29%), focal or diffuse IEDs in 79/125 (63%), bilateral independent IEDs in 11/125 (9%). In 115/125 (92%) brain MRI revealed a clear or subtle lesion. Eighty-five (68%) were seizure-free and drug-free at last follow-up. LEAT, FCD II and HS were more likely to become seizure free/drug free than patients with FCD I and other findings. Age at seizure onset, absence of bilateral independent IEDs, focal lobar/sublobar lesion showed positive correlation with seizure freedom/drug freedom (ODD>1, $p<0.05$). Disease duration, age at surgery, drug resistance and negative MRI presented a negative correlation (ODD<1, $p<0.05$).
Conclusion: We demonstrated the association between surgical outcome and age at surgery, disease duration, drug resistance and pathology, as already reported in literature (Widjaja et al. Neurology 2020;18;94(7):311-321). Studies analyzing pre-surgical variables predicting both seizure freedom/drug freedom after epilepsy surgery are still lacking (Lamberink et al. Lancet Neurol 2020;19(9):748-757). Our study underlines the role of IEDs and brain MRI as predictors of seizure freedom/drug freedom, in a large pediatric series with a good post-surgical outcome and a long follow-up.

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Determinants of functional outcome after pediatric hemispherotomy

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Purpose: Hemispherotomy helps selected children with severe epilepsy to optimize neurodevelopment and functional outcomes through seizure control. We aimed to assess determinants of functional outcome following hemispherotomy undertaken in childhood in a multi-

center large and representative cohort.
Method: We retrospectively analyzed functional outcomes of 455 children who underwent hemispheric surgery in five European epilepsy centers between 2000 and 2016. We identified across-center possible determinants of unaided walking, voluntary grasping with the hemiplegic hand, and speaking (short sentences or age appropriately) through Bayesian multivariable regression modelling with missing data imputation.
Results: 75% children achieved seizure freedom at a mean follow-up of 5.1 years (range 1-17.1). 77% children could walk unaided, 8% could grasp voluntarily, and 68% could speak at the last follow-up. Multivariable analysis identified the following determinants of functional outcome: 1) Children were less likely to walk unaided when diagnosed with hemimegalencephaly (odds ratio (OR) =0.47 [0.25-0.88], p=0.05), had contralateral MRI findings (OR=0.48 [0.27-0.87], p=0.04), experienced recurrent seizures (OR=0.49 [0.28-0.87], p=0.04) or had moderately (OR=0.21 [0.05-0.7], p=0.01) or severely impaired (OR=0.15 [0.04-0.42], p=0.001) intellectual functioning, but were more likely at longer follow-up duration (OR=1.09 [1.03-1.1.16], p=0.02). 2) Children were less likely to grasp voluntarily when diagnosed with Rasmussen encephalitis (OR=0.01 [0-0.14], p<0.001) or Sturge-Weber syndrome (OR=0.02 [0-0.34], p<0.001). 3) Children were less likely to speak when they had contralateral MRI findings (OR=0.37 [0.22-0.64], p=0.004), and longer epilepsy duration (OR=0.79 [0.67-0.92] p=0.01), but more likely when diagnosed with Sturge-Weber syndrome (OR=3.63 [1.54-9.36], p<0.02), were older at surgery (OR=1.42 [1.24-1.65], p<0.001) and had a longer follow-up duration (OR=1.17 [1.11-1.25], p<0.001).
Conclusion: Etiology and bilaterality of structural brain abnormalities are key determinants of functional outcome after hemispherotomy. Not surprisingly, walking and talking ability increases with longer-follow up. Knowledge about independent determinants of functional outcome following pediatric hemispherotomy is crucial for the counselling of patients and families.

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Timing for starting anti-seizure medication withdrawal after epilepsy surgery in adults

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Purpose: More than half of people having epilepsy surgery become seizure-free and may consider withdrawing antiseizure medications (ASMs). There is significant variability in withdrawal procedures and an absence of robust evidence on the ideal timing of postsurgical ASM withdrawal. We compared seizure relapse risk between individuals starting postsurgical ASM withdrawal at different time points.
Method: In this international observational cohort study, including data from ten tertiary epilepsy centers, we included adults who had resective surgery, were seizure-free before starting ASM withdrawal, and had at least one year of follow-up. We compared Kaplan Meier estimates of seizure relapse in those starting ASM withdrawal before years 1, 2, 3 or 4 after surgery versus those who started later. For each comparison, we matched individuals on the propensity to start withdrawing medication to adjust for treatment selection bias.
Results: Of 3366 individuals assessed for eligibility, 952 were included (median [range] post-operative follow-up: 5.6 (IQR 3 - 9.7) years). 465 (49%) individuals started ASM withdrawal during the first year after surgery, 238 (25%) during the second year, 103 (11%) during the third year, 45 (5%) during the fourth year, and 102 (11%) after the fourth year. After matching, there was a higher risk of relapse in those starting withdrawal during the first (HR 1.33, p=0.002) and second (HR 2.18, p<0.001) post-operative years compared to later withdrawal. The risk of seizure relapse did not differ in those starting withdrawals during the third (p=0.22) and fourth (p=0.63) post-operative years compared to those starting later.
Conclusion: Individuals starting ASM withdrawal within the first two post-operative years are at higher risk of seizure relapse than those starting later. There appears to be no advantage for seizure risk in waiting more than two years to start ASM withdrawal following epilepsy surgery.

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All-cause mortality continues to decrease after successful resective epilepsy surgery: a long-term population-based study

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Purpose: To investigate all-cause and epilepsy-related mortality in patients operated with

resective epilepsy surgery in Sweden 1990-2019 and in a comparison group of non-operated patients with drug-resistant epilepsy. We hypothesized that patients who proceed to surgery have lower mortality over time compared to patients who have not been subject to surgical treatment.
Method: Data on 1329 patients (adults and children) from the Swedish National Epilepsy Surgery Register (SNESUR) and 666 patients with drug-resistant epilepsy who had undergone presurgical work-up but not been operated from the same period were analyzed. The operated patients had follow-ups between 2-20 years. We used the Swedish Cause of Death Register to identify deaths. Autopsy reports were collected for patients with suspected SUDEP. Univariate cox regression and multivariable logistic regression were performed to identify predictors for mortality and SUDEP.
Results: SUDEP accounted for one third of all deaths. Surgery was associated with lower all-cause mortality (HR 0.7, 95% CI 0.5-0.9), also when adjusted for age, sex and tonic-clonic seizures at inclusion. The benefit of surgery seemed to persist and possibly increase after very long-term follow-up (15 years). Risk factors of mortality for operated patients were persisting seizures and living alone. Of the operated patients, 37% had seizures, and these had a higher risk of mortality (HR 2.1, 95% CI 1.4-3.0) and SUDEP (HR 3.5, 95% CI 1.7-7.3) compared to patients with seizure-freedom at last follow-up.
Conclusion: In this large, population-based epilepsy surgery cohort, operated patients had a lower all-cause mortality compared to non-operated patients with drug-resistant epilepsy. Seizure freedom in operated patients was the most important beneficial factor for both all-cause mortality and SUDEP.

Epilepsy Surgery 2

11:30 - 12:30

Wednesday, 6 September

Liffey B

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A spatial perturbation framework to validate intracranial electroencephalogram implantation of the epileptogenic zone

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Purpose: One important limitation of intracranial electroencephalography is its limited spatial brain coverage, resulting sometimes in misidentification of the epileptogenic zone (EZ) in focal drug-resistant epilepsy patients due to missing the 'true' seizure-onset zone (SOZ). We devised a method for evaluating the electrode implantation scheme by constructing a spatial perturbation system from channel-level epileptic features to assess network changes be-

tween seizure-free (SF) and non-SF patients when virtually removing the SOZ.
Method: Thirty focal drug-resistant epilepsy patients were analyzed (14 Engel IA, 16 Engel II-IV). Interictal epileptiform discharge (IED), IED-gamma, ripple and fast ripple rates were detected in one-hour continuous NREM sleep segments. The distance from each contact to the channel with the maximum feature rate was computed before and after removing SOZ channels. Since we expect a decaying relationship for unifocal epilepsies (as EZ features decrease, when distant from the EZ), the correlation between feature values and distances were computed. The 'disturbance' is defined as the change in correlation after virtual SOZ removal. It is compared between SF and non-SF patients and is used to classify surgical outcome.
Results: In SF patients, there is a significant network disturbance when using IED-gamma rates (SF: *p=0.002; d=0.96*, non-SF: *p=0.63; d=0.26*), fast ripple rates (SF: *p<0.001; d=0.75,* non-SF: *p=0.28; d=0.22*) and IED rates (SF: *p=0.03; d=0.67,* non-SF*: p=0.25; d=0.28*) to construct the spatial network, whereas it is not observed when using ripple rates (SF: *p=0.42; d=0.26,* non-SF*: p=0.85; d=0.04*). The spatial perturbation framework produced by IED-gamma rates can successfully classify patients with SEEG coverage of the EZ (*p=0.009; AUC=0.85*), whereas IED rates (*p=0.24; AUC=0.66*), ripple rates (*p=0.62; AUC=0.57*) and fast ripple rates (*p=0.15; AUC=0.69*) perform poorly.
Conclusion: The spatial perturbation framework constructed using IED-gamma rates can reliably assess SEEG coverage of the EZ when comparing spatial disturbance after virtual SOZ removal among good and poor outcome patients.

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Personalized whole brain network modelling on virtual epilepsy surgery

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Purpose: We aim to use a personalized whole brain network modelling method to aid clinicians in planning surgical interventions for patients with drug-resistant focal epilepsy.
Method: For each epilepsy patient, we built a patient's specific whole brain network model. The structural scaffold of the patient-specific whole-brain network model is constructed from anatomical T1 and diffusion-weighted magnetic resonance imaging. Bayesian inference methods sample and optimize key parameters of the personalized model using functional stereoelectroencephalography recordings of patients' seizures. These key parameters determine a given patient's personalized model. We performed virtual resection on this patient's personalized models based on the sampling results of Bayesian inference. We compared the results of virtual resection surgery with the outcome of the real surgery. We also introduced an optimization method for surgical strategies.
Results: We gave three patients examples of performing virtual surgery using different clini-

cal hypotheses and real surgery as well. Then we used optimization methods for the surgical strategies. We performed the virtual surgery workflow retrospectively using 40 patients with drug-resistant focal epilepsy. These 40 patients had epilepsy surgery with at least one-year follow-up outcome. We performed the virtual surgery and compared it with the real surgery, which was consistent with the outcome prediction. Based on the personalized whole brain network modelling, we optimized the best surgery strategy. For each patient, we rank the different surgical strategies by the statistical metrics.
Conclusion: Personalized whole brain network modelling can make a prediction on the outcome of surgery and is able to suggest the surgical strategies by ranking the statistical metrics.

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Pathways to epilepsy surgery in a cohort of 85 children with epilepsy associated with tuberous sclerosis complex

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Purpose: To describe the clinical features and presurgical assessment leading to epilepsy surgery, as well as the long-term outcomes of children diagnosed with epilepsy associated with tuberous sclerosis complex, by conducting a retrospective cohort study covering the practice of the last twenty years.
Method: We identified 85 children born after January 2000 and diagnosed with tuberous sclerosis complex and epilepsy through the complementary matching of two exhaustive registries of genetic diseases followed by a review of the medical records within two French neuropediatric centers. Demographic, clinical, and longitudinal data including seizure types and frequency, anti-seizure medications used, and cognitive assessment were collected. In patients who underwent presurgical evaluation, invasive recordings, and/or resective surgery, we described the characteristics and long-term outcomes associated with these procedures.
Results: Resective surgery was considered in 40 % of the children of the cohort and performed in 19 % of cases, most often before the age of four (median age: 3.5 y. min: 2 mo.

max: 13y.). Seizure freedom was achieved in 57 % of cases one year after surgery, and in 43 % ten years after. The number of anti-seizure medications required decreased in 50 % of cases after surgery. Infantile spasms, intellectual disability, autism spectrum disorder or severe behavioral disorders were not contraindications to surgery. However, they were associated with an increased rate of complications and a lower seizure freedom rate. A decrease of seizure frequency and number of anti-seizure medications was also observed within drug-resistant patients who did not proceed to surgery after initial evaluation.
Conclusion: The assumption of complex multifocal epilepsy can be misleading in the context of young children, since surgical treatment allows equivalent results to those obtained in other populations of patients with drug-resistant epilepsy, and is associated with a reduction of the burden of anti-seizure medications which is crucial in young, developing children

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Clinical yields of ultra-long sub-cutaneous EEG monitoring in drug-resistant focal epilepsies

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Purpose: Seizure assessment with patient diaries has been shown to be highly unprecise. We used a novel EEG recording device (subcutaneous EEG–sqEEG) that collects EEG signal by a subcutaneous electrode to perform ultra-long seizure monitoring in epilepsy patients to assess seizure frequency and effects of antiseizure medications (ASM) modifications.
Method: Three patients with drug-resistant focal epilepsy were recorded for 4 months. The sqEEG electrode was implanted on the side of the focus, as previously assessed. Concordance of scalp EEG and sqEEG in seizure recording was evaluated in EMU. Seizure frequency by patient's diary and sqEEG evaluation (by visual and automatic detection analysis), and treatment adjustments were performed every month.
Results: Patient 1: right focal cortical dysplasia. Concordance in EMU between visual inspection and automatic analysis of sqEEG (Cvisual/sqEEG) was 100%. The patient's diary reported only 85% of seizures detected by sqEEG; sqEEG documented a mild improvement of seizure frequency following ASM increments. Patient 2: MRI negative. Cvisual/sqEEG was 100%. Patient's diary reported 66.6% of seizures detected by sqEEG. SqEEG showed a mild improvement (inferior to patient's evaluation) following ASM adjustments. Patient 3: right MTS, bilateral seizure onset. In EMU clinical and frequent subclinical seizures were observed. He was implanted bilaterally. Cvisual/sqEEG was 83% in the left, 54% in the right side. Twenty seizures were reported by the patient, none of them detected by visual inspection or auto-

matic detection. SqEEG recorded 64 seizures (right: left=6:1). Distinction between subclinical and clinical seizures was not possible. SqEEG showed no seizure improvement following ASM adjustments.
Conclusion: SqEEG allowed to detect a higher number of seizures as compared to patients' diaries and to assess effects of ASM adjustments. Cvisual/sqEEG was more consistent in seizures with overt clinical/EEG ictal features as compared to subclinical seizures. Bilateral implantation provided previously unknown information on side of seizure predominance.

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Clinical information informs automated detection of focal cortical dysplasia

L Walger[1], B David[1], F Schuch[1], T Baumgartner[1], J Witt[1], A Racz[1], R von Wrede[1], V Borger[2], H Vatter[2], C Helmstaedter[1], C Elger[1], A Radbruch[3], M Reuter[4], R Surges[1], T Rüber[1] [1]University Hospital Bonn, Department of Epileptology, Bonn, Germany, [2]University Hospital Bonn, Department of Neurosurgery, Bonn, Germany, [3]University Hospital Bonn, Department of Neuroradiology, Bonn, Germany, [4]DZNE, Bonn, Germany

Purpose: Presurgical evaluation for patients with Focal Cortical Dysplasia (FCD) yields negative results in up to one-half of all cases. Current computational approaches for localizing FCDs only use MRI data. In clinical practice, however, other diagnostic modalities can play an essential role. We aim to utilize non-imaging modalities as an additional input for an Artificial Neural Network to improve FCD localization and segmentation.
Method: We retrospectively collected data from 146 patients with suspected FCD, which included MRI data, interictal and ictal EEG descriptions, semiology and neuropsychological testing. We then extracted a hypothesis about affected brain regions and translated them into volumetric binary masks.The single attention 3D UNet model by (Oktay et al. *arXiv 2018:1804.03999*) is the basis of our model and we trained two networks, one with MRI data alone (MRI-NN) and one with MRI and clinical data combined (Clinical-NN). We additionally used a published network as baseline model (David et al. Epilepsia 2021:1005-1021)
Results: Clinical-NN achieves a higher DICE score (0.302 ±0.163) than the other two models. On a patient level, our networks are more sensitive than the baseline model. Especially when the majority of clinical information is available, Clinical-NN performs much better with a detection rate of 84%, compared to 76% for MRI-NN and 60% for the baseline model. When clinical information is inconclusive or missing, however, Clinical-NN performs worse than MRI-NN (57% vs. 63%). Per lesion, Clinical-NN is also more specific than MRI-NN, which produces small spurious clusters, but the baseline model achieves the highest specificity.
Conclusion: We have shown how utilizing non-imaging modalities can aid the detection and segmentation of FCDs. This work represents the first step towards modelling the interplay between these modalities by computational means. The dependency of performance on the presents of conclusive clinical information hints at our model learning to integrate such data.

Genetics 1

15:30 - 16:30
Sunday, 3 September
Liffey Hall 2

1235

The genetic landscape across more than 1000 surgically accessible epileptogenic human brain lesions

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Purpose: Understanding the exact molecular mechanisms involved in the etiology of epileptogenic pathologies with or without tumour activity is essential for improving treatment of drug-resistant focal epilepsy.
Method: We will present a joined analysis including epileptogenic brain lesions that were deep sequenced to discover novel lesion-gene associations and explore genotype-phenotype associations. In a preliminary analysis, we characterize the landscape of somatic genetic variants in resected brain specimens from 650 individuals with drug-resistant focal epilepsy using deep whole-exome sequencing (>350×), whole-genome genotyping and ultra deep panel sequencing.
Results: We observe a greater number of somatic single-nucleotide variants (SNV) in low-grade epilepsy-associated tumours (LEAT) than in brain tissue from malformations of cortical development (MCD) or hippocampal sclerosis (HS). Tumour tissues also had the largest number of likely pathogenic variant carrying cells. LEAT had the highest proportion of samples with one or more somatic copy number variants (CNV; 24.7%), followed by MCD (5.4%) and HS (4.1%). Recurring somatic whole chromosome duplications affecting Chromosome 7 (16.8%), chromosome 5 (10.9%), and chromosome 20 (9.9%) were observed among LEAT. For germline variant associated MCD genes such as *TSC2, DEPDC5*, and *PTEN*, germline SNV were frequently identified within large loss of heterozygosity regions, supporting the recently proposed 'second hit' disease mechanism in these genes. We detect somatic variants in twelve established lesional epilepsy genes and demonstrate exome-wide statistical support for three of these in the etiology of LEAT (e.g., *BRAF*) and MCD (e.g., *SLC35A2* and *MTOR*). We also identify novel significant associations for *PTPN11* with LEAT and NRAS Q61 mutated protein with a complex MCD characterized by polymicrogyria and nodular heterotopia.

Conclusion: Our comprehensive genetic screen sheds light on the genome-scale landscape of genetic variants in epileptic brain lesions, informs the design of gene panels for clinical diagnostic screening. At the conference we will present new gene associations and genotype-phenotype analyses.

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Pathogenic *GABRA3* variants lead to dominant or recessive X-linked disorders depending on functional outcomes

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Purpose: The X-linked *GABRA3* gene has only been described as pathogenic in very few individuals, who displayed phenotypes ranging from severe developmental and epileptic encephalopathy to intellectual disability without seizures and even unaffected carriers. Based on functional analyses, the pathomechanism has so far been concluded to be loss-of-function (LOF). We collected a cohort of published (20) and unpublished (15) individuals carrying *GABRA3* variants and aimed to describe the correlation between functional outcome and phenotype.

Method: Through an international collaboration and literature search, we collected a cohort

of 35 individuals with *GABRA3* variants. Data on genotype, family history and phenotype were collected in a standardized manner. α3-subunit missense variants were investigated in combination with β3 and γ2 subunits in α3β3γ2 receptor assemblies. To ensure uniform expression of homogenous receptor populations, pentameric concatenated constructs were designed to contain either two wildtype, one wildtype and one variant, or two variant α3 subunits, reflecting both the heterozygote and homozygote conditions.
Results: Using the functional outcomes, we stratified the cohort into three groups: a) those carrying a GOF variant, b) those carrying a LOF variant and c) those carrying a neutral variant. In agreement with other $GABA_A$ receptor genes, we found distinct phenotypic differences between individuals carrying missense *GABRA3* GOF variants opposed to those carrying missense or nonsense *GABRA3* LOF variants.
With GOF variants, males and females were all affected, all males had epilepsy and severe ID, cortical visual impairment, and no spoken language.
With LOF variants, males were affected, while females were healthy carriers. Male LOF variant carriers displayed a milder phenotype with normal to moderate intellectual disability, behavioural disorders and delayed language development.
Conclusion: With this large cohort of individuals with *GABRA3* variant we show that variants may result in both GOF and LOF, and that this functional discrepancy is reflected in the phenotypic outcome of the affected individuals.

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Gain-of-function and loss-of-function *GRIA3* variants lead to distinct neurodevelopmental phenotypes

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Purpose: AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor is a voltage gated ion-channel critical for most brain functions. AMPARs are encoded by *GRIA1-4* genes. *GRIA3* is X-linked, and females are presumed to be healthy carriers. Few patients with GRIA3-related disorder are reported and functional testing is lacking. We aimed to deep-phenotype GRIA3-related disorders, functionally test *GRIA3* variants in order to proof pathogenecity and identify clinical biomarkers that predict functional and clinical outcomes.
Method: Patients with *GRIA3* variants were recruited through an international collaboration of epilepsy/genetics research groups. Medical information was collected from local physicians. *GRIA3* variants were introduced in a vector using site-directed mutagenesis and injected in *Xenopus laevis* oocytes and HEK293 cells. Voltage-clamping electrophysiology was used to measure effects on AMPAR currents. Clinical biomarkers were identified by comparing functional outcomes with clinical phenotypes.
Results: We included 25 patients (11 females) carrying 17 different variants. Ten patients carried a gain-of-function (GoF) variant while 15 presented with loss-of-function (LoF) variants. Remarkable differences between the GoF and LoF patient cohorts were identified. GoF variants were associated with more severe outcomes; patients were significantly younger at time of seizure onset (median age 1 month), hypertonic, and more often had movement disorders including hyperexplexia. In contrast, patients with LoF variants were older at time of seizure onset (median age 16.5 months), hypotonic, and had sleep difficulties. LoF and GoF variants were disease causing in both genders but affected males often carried *de novo* or inherited hemizygous LoF variants whereas affected females harboured *de novo* heterozygous GoF variants.
Conclusion: This dataset represents the largest clinical and functional evaluation of missense variants in any *GRIA* gene. We created a predictive tool that can be used to determine whether a *GRIA3* variant may impose a loss- or gain-of-function effect on AMPAR function. Our data also shows that females can be affected.

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Long-term evolution of *SCN8A*-related conditions: focus on transition age

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Purpose: *SCN8A* pathogenic variants can cause a wide range phenotype, mainly consisting of epilepsy and neurodevelopmental disorders. We aimed at investigating the long-term evolution of *SCN8A*-related conditions, focusing on the critical time of transitioning from childhood to adulthood, to identify clinical trajectories and assess transition from pediatric to adult care services.
Method: Individuals carrying a pathogenic *SCN8A* variant, aged ≥14 years, were recruited through an international clinical network. Electroclinical data were collected through ad hoc questionnaires and phenotyping sheets, including a transfer history form. Functional independence was evaluated through Barthel Index for ADL and general functioning through the Children's Global Assessment Scale.
Results: We collected 42 subjects, aged 14-55 years (mean age: 24.9); 19/42 (45.2%) have completed the transition at a mean age of 19.2 years (range 17-25 years). The main issues at transition regarded seizure management (50%); polytherapy (42.8%); ADLs impairment (42.8%), neurodevelopmental disorders (40.4%); psychiatric comorbidities (35.7%), behavioural problems (35.7%); multidisciplinary care (23.8%); social support (19%); contraception (16.6%); compliance, legal issues (9.5%); bone health (9.5%); diagnostic difficulties (9.5%). Patients belonging to milder phenotypes (benign familial infantile epilepsy, BFIE), may not need transition, as symptoms usually resolve in childhood. However, clinicians should be aware of the possible late onset of movement disorders. Patients with *SCN8A*-developmental and epileptic encephalopathy need life-time multidisciplinary care, that should be delivered in specialized centers without age limitations, with a holistic approach. Patients with intermediate epilepsy had heterogeneous trajectories, where transition could be diversified accordingly. Patients without epilepsy require equal attention during transition, especially as regards care and support needs for movement or behavioural disorders as well as cognitive impairment.
Conclusion: The main *SCN8A* phenotypic subgroups have distinct clinical characteristics and needs that should be reflected in the care process, upon all life stages. We propose a diversified transition model aiming at precision in all contexts of care.

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HCFC1 variants in the proteolysis domain are associated with X-linked idiopathic focal epilepsy: exploring the underlying mechanism

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Purpose: *HCFC1* encodes transcriptional co-regulator HCF-1, which undergoes an unusual proteolytic maturation at a centrally located proteolysis domain. *HCFC1* variants were associated with X-linked cobalamin metabolism disorders and mental retardation-3. This study aimed to explore the role of *HCFC1* variants in common epilepsy and the mechanism underlying phenotype heterogeneity.
Method: Whole-exome sequencing was performed in a cohort of 313 patients with idiopathic partial (focal) epilepsy. Functional studies determined the effects of the variants on the proteolytic maturation of HCF-1, cell proliferation, and *MMACHC* expression. The role of *HCFC1* variants in partial epilepsy was validated in another cohort from multiple centers.
Results: We identified seven hemizygous *HCFC1* variants in 11 cases and confirmed the finding in the validation cohort with additional 13 cases and six more hemizygous variants. All patients showed partial epilepsies with favorable outcome. None of them had cobalamin disorders. Functional studies demonstrated that the variants in the proteolysis domain impaired the maturation by disrupting the cleavage process with loss of inhibition of cell growth but did not affect *MMACHC* expression that was associated with cobalamin disorder. The degree of functional impairment was correlated with the severity of phenotype. Further analysis demonstrated that variants within the proteolysis domain were associated with common and mild partial epilepsy, whereas those in the kelch domain were associated with cobalamin disorder featured by severe and even fatal epileptic encephalopathy, and those in the basic and acidic domains were associated with mainly intellectual disability.
Conclusion: *HCFC1* is potentially a candidate gene for common partial epilepsy with distinct underlying mechanism of proteolysis dysfunction. The HCF-1 domains played distinct functional roles and were associated with different clinical phenotypes, suggesting a sub-molecular effect. The distinct difference between cobalamin disorders and idiopathic partial epilepsy in phenotype and pathogenic mechanism, implying a clinical significance in early diagnosis and management.

Genetics 2

11:30 - 12:30
Wednesday, 6 September
Liffey A

723

Clinical phenotypes of patients with *GABRG2* loss-of-function and gain-of-function variants

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Purpose: Patients harbouring *GABRG2* variants have been associated with a broad phenotypic spectrum ranging from febrile seizures to developmental and epileptic encephalopathies (DEE). To date, *GABRG2* variants have only been shown to cause loss-of-function (LoF) effects, which leads to reduced neuronal GABAergic activity. Gain-of-function effects have recently been observed in closely related *GABR* subunits. We performed a clinical, genetic and functional evaluation of patients carrying *GABRG2* variants.
Method: Patients were ascertained via an international network using demographic, genetic and electro-clinical data. Thirty-nine unpublished patients were included harbouring 27 variants. Fifteen were missense and functionally characterized by comparing $GABA_A$ receptors containing wild-type versus variant *GABRG2* subunits using whole-cell voltage clamp electrophysiological recordings.
Results: Twenty variants showed a LoF effect and two a GoF effect. Five variants displayed no functional alterations and the seven patients harbouring these were omitted from further analysis. The most severely affected children (n=2) were GoF, with epilepsy onset within 3 months of life, severe DEE, focal seizures and severe hypotonia. A third patient with a variant causing GoF showed mild developmental delay (DD), mild hypotonia and autism. Twenty-nine patients with LoF variants showed seizure onset between 3 months and 10 years, with febrile seizures in 3/29 (10%) and epilepsy in 26/29 (90%: generalized 73%, focal + generalized 19% and focal 8%): 42% had genetic epilepsy with febrile seizures +, 23% DEE, 8% myoclonic atonic epilepsy, 4% myoclonic absence epilepsy, 4% childhood absence epilepsy, 4% juvenile absence epilepsy and 15% unclassified epilepsy. They showed psychiatric and behavioural disturbances in 48%, mild hypotonia in 7% and DD in 34% (mild in 70%).
Conclusion: *GABRG2* LoF variants are associated with a phenotypic spectrum ranging from febrile seizures to DEE. In addition, our study provides the first evidence of *GABRG2* GoF variants and propose distinct phenotypic features that differ from those related to LoF variants.

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Somatic mutations as a cause of drug-resistant epilepsy including hippocampal sclerosis

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Purpose: Advances in sequencing technologies has driven genetic discovery in epilepsy. The contribution of somatic variants to epilepsy has recently been demonstrated, particularly in the aetiology of malformations of cortical development (MCD). The aim of this study was to determine the diagnostic yield of somatic variants in somatic and germline epilepsy genes, ascertained from resected brain tissue from patients with multi-drug resistant focal epilepsy.
Method: Forty-two cases were recruited across three categories; (i) MCD, (ii) mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) and (iii) non-lesional focal epilepsy. Participants were sub-divided based on histopathology of the resected brain. Paired blood- and brain-derived DNA samples were sequenced using high-coverage targeted next-generation sequencing to high depth (585X and 1360X respectively). Variants were identified using Genome Analysis ToolKit (GATK4) MuTect-2 and confirmed using high-coverage Amplicon-EZ sequencing.
Results: Forty-one patients were successfully sequenced using the NGS pipeline. Four variants were validated using Amplicon sequencing – *CBL* and *ALG13* in the MTLE-HS group: *MTOR* and *FLNA* in the MCD group. The overall diagnostic yield across 41 patients was 10% - 9% in HS and 20% in MCD (FCD).
Conclusion: This study provides novel insights into the aetiology of MTLE-HS, for the first time highlighting a potential pathogenic role of somatic variants in *CBL* and *ALG13*. We also report for the first time pathogenic somatic variants in *FLNA* in MCD. We provide further insight into the importance of *MTOR* in MCD, in particular focal cortical dysplasia. This work demonstrates the diagnostic value of somatic variants in germline and somatic epilepsy genes, and the potential importance of genetic analysis of resected epilepsy surgery brain tissue.

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Natural history and adult phenotype of *SYNGAP1*-DEE

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Purpose: *SYNGAP1* variants are associated with rare developmental and epileptic encephalopathies (DEEs). While *SYNGAP1*-related childhood phenotypes and daily living abilities have recently been described, the adult phenotype remains ill-defined.
Method: Patients 18 years or older with likely pathogenic and pathogenic (LP/P) *SYNGAP1* variants were recruited via physicians' practices and patient organization groups with diverse geographic locations. We used validated questionnaires to evaluate:
-Seizure severity using a modified version of the Severity Assessment (SA) tool
-Social communication deficits using Social Communication Questionnaire Lifetime Version
-Adaptive behavioural abilities using Vineland Adaptive Behavioural Scales 3
Statistical analysis was performed using Kruskal-Wallis test to compare assessment scores with *SYNGAP1* variant types**.**
Results: -14 adult patients harboured novel LP/P *SYNGAP1* variants.
-Comorbidities seen: abnormal pain processing (100%), sleep disturbances (86%), social communication disorder (79%), aggressive behaviour (79%), self-injurious behaviours (86%).
-Self-injurious behaviour and aggression were the most important factors increasing caregivers' burden.
-Myoclonic-atonic seizures are uncommon in adults.
-One patient with a indel of *SYNGAP1* exon 3 demonstrated an elevated ability to carry out daily living skills, as well as stronger social skills compared to the rest of the cohort.
-We describe the oldest patient with *SYNGAP1* reported so far (65-years-old) as well as the natural history of her symptoms.
Conclusion: Adults with *SYNGAP1*-related DEEs present variable seizure frequency, but myoclonic-atonic seizures are less prevalent in adults compared to children previously reported in the literature. Adult patients were able to function slightly more independently than historical pediatric patients but were still very dependent for activities of daily living. Non-seizure comorbidities, especially aggression, represent serious concerns and remain significant challenges for both patients are caregivers.

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Variants in SLCO5A1 and synaptic assembly genes contribute to impulsivity in juvenile myoclonic epilepsy: genome wide association study

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Purpose: Elevated impulsivity is a key component of attention-deficit hyperactivity disorder (ADHD), bipolar disorder and epilepsy. Impulsivity is an endophenotype of juvenile myoclonic epilepsy (JME). Neural networks underlying impulse control and myoclonic seizures overlap and may share genetic influences. There has been no GWAS of impulsivity in any neuropsychiatric disorder.
Method: We performed a genome-wide association, colocalization and pathway analysis of trait impulsivity in JME. We investigated the influence of 8,950,360 variants on impulsivity in European ancestry JME patients (n=324) and a mega-analysis with all ancestries (n=372), who self-rated their trait impulsivity using the Barratt Impulsivity Scale, eight-item BIS-Brief version. We first conducted a GWAS of BIS-Brief score in the European subset, adjusted for sex, genotyping batch, age at consent, population stratification, and seizure frequency.
Results: We identify genome-wide associated SNPs at 8q13.3 ($p=7.5 \times 10-9$) and 10p11.21 ($p=3.6 \times 10-8$). The 8q13.3 locus colocalizes with SLCO5A1 expression quantitative trait loci in cerebral cortex ($p=9.5 \times 10-3$). SLCO5A1 codes for a membrane-bound organic anion transporter and upregulates synapse assembly/organisation genes. Pathway analysis also demonstrates 9.3-fold enrichment for synaptic assembly genes (p=0.03) including NRXN1, NLGN1 and PTPRD. RNAi knockdown of Oatp30B, the Drosophila homolog of SLCO5A1, causes both over-reactive startling behaviour ($p=8.7 \times 10-3$) and increased seizure-like events ($p=6.8 \times 10-7$). Polygenic risk score for ADHD correlates with impulsivity scores ($p=1.60 \times 10-3$), demonstrating shared genetic contributions.
Conclusion: We present evidence for the role of SLC05A1 in impulsivity and seizure susceptibility through triangulation with GWAS, colocalization with gene expression and functional evaluation using an established model of seizure susceptibility in Drosophila. SLCO5A1 loss-of-function represents a novel impulsivity and seizure mechanism. Synaptic assembly genes may inform the aetiology of impulsivity in health and disease. Excitatory-inhibitory imbalance in the prefrontal-striatal network may predispose to epilepsy and impulsivity substrates and invites new approaches to neuromodulation of generalised seizures.

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Analysis of more than 90,000 diagnostic tests in people with epilepsy identifies the age of seizure onset-specific epilepsy-associated genes

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Purpose: Gene expression follows temporal patterns in the human brain. In the ILAE Epilepsy Classification, epilepsies are classified according to seizure onset. An additional criterium represents the etiology, such as genetic factors. Here, we systematically assessed the seizure onset specificity across epilepsy-associated single-gene disorders using the largest resource of clinical genetic data to date.
Method: We extracted genetic variants from 1,643,781 diagnostic test results in people with epilepsy annotated in the largest genetic test repository ClinVar. To overcome roadblocks in using public resources for genotype-phenotype analysis, we utilized the Mondo clinical term ontology and developed a framework to map Mondo terms to the ILAE Classification of Epilepsy and of Epilepsy Syndromes. Gene-seizure onset enrichment analyses were performed for all variants combined and on variant type level.
Results: Across the whole ClinVar database, we identified 89,453 variants in 549 genes in total and 11,731 pathogenetic (likely pathogenic and pathogenic combined) variants in 415 genes in people with epilepsy. The neonatal/infantile-onset (NIO) group had the highest number of genes (n=186) and pathogenic variants (n=4319). The genes with the largest number of pathogenic variants were *SCN1A* in the NIO group (N= 1049), *GRIN2A* in the childhood-onset (CO) group (N=168), *LGI1* in the adolescent/adult-onset (AAO) group (N=36), and *DEPDC5* in the variable-onset (VO) group (N=200). In variant type analysis, the VO group was enriched for protein-truncating variants (OR 2.24, 95%CI 1.9-2.63, $p < 0.001$) and the NIO group – for missense variants (OR 1.93, 95%CI 1.69-2.21, $p<0.001$).
Conclusion: This is the largest analysis of clinical genetic data from people with epilepsy to date. We identified gene sets associated with age-specific epilepsy syndromes, found new genotype-seizure onset associations, and validated the existing ones. At time of conference, we will present additional analysis using the rich set of data available in combination with biological data such as transcriptomic and pathways data.

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Developmental and epileptic encephalopathies associated with gain-of-function *GABRB3* variants are more severe than those with loss-of-function

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Purpose: Patients with developmental and epileptic encephalopathies can present with variants in genes coding for GABAA receptors. These variants have typically been presumed to cause loss-of-function receptors leading to reduced neuronal GABAergic activity. Yet, patients with GABAA receptor variants have an unusually diverse set of clinical phenotypes. We aimed to unravel the reasons for the diverse phenotypic spectrum found in patients with *GABRB3* variants.
Method: Through international collaboration and literature search, we collected a cohort of 88 individuals with *GABRB3* variants. Data on genotype, family history and phenotype were collected in a standardized manner. Fifty-four β3-subunit missense variants were investigated functionally in α1β3γ2 receptor assemblies using electrophysiology. Furthermore, desensitization properties of 20 gain-of-function *GABRB3* variant receptors were evaluated.
Results: We determined that pathogenic *GABRB3* missense variants functionally segregate into gain-of-function and loss-of-function groups. Distinct clinical phenotypes emerged when comparing 27 patients in the gain-of-function cohort to 47 in the loss-of-function cohort. The gain-of-function cohort presented with a significantly younger age of seizure onset (median 2.5 months vs 11 months; $p<0.0001$) and higher risk of severe intellectual disability (odds ratio 80; $p<0.0001$). Microcephaly was exclusively reported in the gain-of-function cohort (55%) while febrile seizures at onset were exclusively reported in the loss-of-function cohort (32%). Analysis of receptor desensitizing properties revealed that gain-of-function variants with the most severe manifestations of the disorder reduced receptor desensitization thereby further increasing GABAergic activity to exacerbate the clinical phenotype. This included younger age of first seizure onset (median 0.5 months), movement disorders (dystonia and dyskinesia), epilepsy of infancy with migrating focal seizures (EIMFS) and risk of early mortality.
Conclusion: Overall, patients with *GABRB3* variants that increase GABAergic activity have more severe forms of developmental and epileptic encephalopathies. Furthermore, we find that gain-of-function variants can increase or decrease receptor desensitization properties and that this modulates the degree of disease severity.

Neuroimaging
15:30 - 16:30
Sunday, 3 September

Liffey Hall 1

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Atrophy in subcortical brain structures in newly diagnosed focal epilepsy is associated with alterations in white matter connectivity and neuropsychology

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Purpose: Subcortical atrophy has been reported in patients with chronic focal epilepsy. Preliminary evidence indicates that these changes may already present at diagnosis. However, it is unclear whether localised subcortical shape deformations account for atrophy in patients with newly diagnosed focal epilepsy (NDfE) and whether such changes are associated with white matter pathways and neuropsychological function which is also known to be compromised before the start of antiepileptic drug treatment (AED).
Method: We collected T1-weighted and diffusion-weighted MRI, and neuropsychological data from 85 patients with NDfE and 34 healthy controls (HC) matched for age, sex and education. A vertex-based shape analysis was performed to compare NDfE and HC. With a linear combination (PCA) of significant subcortical shape values, we used a connectometry analysis to identify white mater pathways related to subcortical shape alterations. The relationships between subcortical values and neuropsychology were assessed using a generalised-canonical-correlation approach.
Results: We found bilateral focal inward deformation (atrophy) in areas of the thalamus and pallidum, and in the right hippocampus and brain stem in NDfE compared to HC. The connectometry analysis revealed that increased quantitative anisotropy (QA) was associated with overall shape variation in a number of tracts including the anterior commissure and corpus callosum forceps major (FDR = 0.0002), as well as a decreased QA in the fornices and left arcuate fasciculus (FDR = 0.09). Inward deformation in the thalami and right pallidum was related to negative mood and reduced working memory and processing speed abilities.
Conclusion: Atrophy of subcortical structures previously associated with the generation and maintenance of focal seizures may be present at epilepsy diagnosis and correlated with alterations in white mater connectivity and neuropsychology. Together findings suggest that changes are at least partly the result of early epileptogenic processes rather than due to the chronicity and AED treatment.

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Localization of temporal lobe epilepsy networks from individualized atrophy patterns

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Purpose: Hippocampal atrophy is associated with temporal lobe epilepsy (TLE), but it remains unclear why patients show heterogenous structural compromise beyond the seizure focus. Here, we tested whether the regional variability in atrophy patterns at the single-subject level maps to a common brain network.
Method: We studied 83 adult patients with drug resistant TLE (39 males, mean age±SD=30.2±10.3 years) and 120 healthy controls (54 males, mean age±SD=29.8±9.5 years). All participants underwent high-resolution T1w MRI.
We performed a whole-brain, voxel-based morphometry analysis in controls to generate a normative model of atrophy. Beta-term maps for age and gender, as well as the map of the residuals from this normative model, were used to calculate a *w*-score for grey matter concentration (henceforth, atrophy) in each patient. Individualized *w*-maps were thresholded to retain the top 1% of atrophied voxels. The brain network functionally connected to each patient's peak atrophy locations were then computed using human brain connectome data (n=1000).
Results: Individuals with TLE showed widespread atrophy, spanning cortical, subcortical, and cerebellar territory, with a maximum overlap in the ipsilateral anterior hippocampus (maximum patient overlap of 25%). However, these heterogeneous atrophied regions were part of a common brain network defined by functional connectivity to the mesiotemporal lobe, sensorimotor cortex, basal ganglia, and cerebellum. Comparing subject-specific atrophy network maps in patients to controls revealed that atrophy locations in TLE had increased functional connectivity to mesiotemporal, basal ganglia, and cerebellar structures, but decreased functional connectivity to sensorimotor cortices (p_{FDR}<0.01), suggesting that different functional mechanisms may underlie atrophy patterns in the disease.
Conclusion: Our findings highlight the utility of atrophy network mapping to localize syndrome-specific brain networks despite inter-individual morphological heterogeneity. Personalized atrophy network mapping promises to enhance diagnostics and patient subtyping efforts in TLE and may guide the calibration and prognostics of surgical and neuromodulatory treatments.

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Anti-seizure medications may not influence brain morphometry in mesial temporal lobe epilepsy: a prospective MRI study

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Purpose: In existing literature on epileptic syndromes, the administration of one or more anti-seizure medications (ASMs) is considered a potential confounding factor for neuroimaging findings regarding brain structure and function. In this work, we assessed differences in cortical and subcortical grey matter among drug-naive patients with mild MTLE, patients undergoing monotherapy, and healthy controls. Furthermore, we evaluated longitudinal changes in brain morphology in a subset of patients with a follow-up MRI exam.
Method: We consecutively enrolled 57 patients with mild MTLE and 58 healthy controls. Twenty-two out of 57 patients were drug-naïve (39.8±14.2 years), while 35/57 (36.8±12.2 years) were treated with one ASM (12/35 carbamazepine, 8/35 lamotrigine, 1/35 oxcarbazepine, 7/35 levetiracetam, 5/35 topiramate and, 2/35 valproate). All subjects underwent 3T-MRI and *FreeSurfer* was used for automated cortical and subcortical morphometry. Eight mild MTLE patients also underwent a follow-up MRI (mean distance between scans: 4.0±3.3 years). Differences in cortical and subcortical grey matter between naïve and on-treatment mild MTLE patients compared to healthy controls were assessed using one-way Analysis of Covariance (ANCOVA), with age, disease duration and intracranial volume as covariates-of-no-interest. The longitudinal analysis was conducted constructing a linear mixed model with a first-order autoregressive structure.
Results: No significant differences in cortical and subcortical grey matter were found between drug-naïve and treated mild MTLE patients. Moreover, in mild MTLE patients, progressive atrophy involving thickness of right insula (p=0.007) and surface of left inferior parietal gyrus (p=0.006), precuneus (p=0.006), and superior parietal gyrus (p=0.001) was observed.
Conclusion: Our study contributes to delineate the role of ASMs on brain structure, in a group of patients with up to ten years of history of medication. The lack of ASMs effect on cerebral grey matter reassures about the safety of most used drugs in focal epilepsy and on their potentially marginal role in influencing neuroimaging results.

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Structural correlates of drug resistance in juvenile myoclonic epilepsy

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Purpose: MRI studies on idiopathic generalized epilepsies have described structural changes in patients compared to healthy controls but have not clarified which ones may relate to sei-

zure activity. Here we assessed surface-based MRI markers of cortical morphology in juvenile myoclonic epilepsy (JME) to identify structural correlates of drug resistance.
Method: In this cross-sectional multicentre analysis, we obtained 3T MRI from a total of 78 controls (56% female, median age 26 [22, 32]), 42 drug-resistant patients (50% female, median age 26 [22, 32]) and 37 drug-responsive (59% female, median age 32 [25, 39]), recruited at two tertiary epilepsy centres. Drug resistance was defined as failure to attain seizure freedom in the last 12 months despite two adequate trials of anti-seizure medication. Datasets were corrected for batch effects and processed through a framework that integrates cortex-wide markers of vertical (thickness) and horizontal cortical organization (surface area) as well as sulco-gyral complexity (gyrification index). We performed a vertex wise analysis with a cluster defining threshold of p=0.025. Cognitive performance on executive functions and verbal memory was also assessed.
Results: Compared to controls, patients showed cortical thinning and increased surface area in the temporal and prefrontal regions after cluster correction. Drug-resistant patients showed increased surface area in prefrontal, cingulate and temporal cortex accompanied by increased gyrification in the temporal cortex when compared to drug-responsive patients. Finally, patients with drug resistance disease performed worse than drug sensitive patients and controls across tests of verbal fluency ($p<0.05$) and mental flexibility ($p<0.05$) and showed higher anxiety ($p<0.05$) and depression scales ($p<0.001$).
Conclusion: Drug-resistant patients with JME present a distinct structural phenotype characterized by increased surface area and gyrification. These features are likely to be part of a continuum of neurodevelopmental abnormalities reflecting increased seizure predisposition and neurocognitive deficits.

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Segmenting focal cortical dysplasias using graph neural networks: a MELD study

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Purpose: Focal cortical dysplasia (FCD) is a common cause of drug-resistant epilepsy, and accurate detection on MRI is critical for presurgical planning. However, identification of FCD remains challenging due to its subtle imaging features. Previous detection methods have been susceptible to high numbers of false positives due to their inability to consider the entire cortex. This Multicentre Epilepsy Lesion Detection (MELD) project study aimed to develop a whole brain graph neural network (GNN) for segmenting FCDs.
Method: The MELD cohort of surface-based MRI features for 618 patients with FCD and 397 controls was used to train and test a novel GNN model. The cortical mesh was represented as a graph, treating vertices as nodes connected to neighbouring vertices by edges, enabling the network to learn spatial relationships between brain regions. The model was trained to identify lesional vertices. It was pretrained with synthetic lesions and fine-tuned with real

patient data. We combined three different loss functions: Dice loss, cross-entropy loss, and a distance-based loss which allowed for uncertainty in manually defined lesion masks.
Results: On a withheld test cohort, the GNN model achieved a sensitivity of 67% in patients, with a specificity of 70% in controls, a significant gain in specificity in controls against patch-based approaches on the same dataset (sensitivity 67%, specificity 59%). The GNN model decreased the number of false positive clusters from a median of 1 per patient [IQR: 0-3] to 0 [IQR: 0-1].
Conclusion: In conclusion, we demonstrate the utility of GNNs for FCD segmentation in MRI scans and the potential benefit of using synthetic data for pre-training. The fully trained GNN substantially improved on previous patch-based approaches. Further improvements are likely to result from additional measures to mitigate lesion mask uncertainty. This improvement of specificity is important for clinical integration of lesion-detection tools, reducing the number of areas requiring expert review.

Neuropsychology

11:30 - 12:30
Wednesday, 6 September
Liffey Hall 2

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Neuropsychological outcomes following stereo-EEG radiofrequency thermocoagulation

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Purpose: Radiofrequency thermocoagulation (RF-THC) has been posed as relatively safe from a cognitive perspective, however, this tends to be reported in the absence of neuropsychological assessments. The current study is the first prospective evaluation of neuropsychological outcomes associated with stereo-EEG RF-THC in patients with focal drug resistant epilepsy.
Method: Thirty-eight stereo-EEG candidates (*M*=36.47 years, *SD*=10.10, 56% female) were prospectively recruited across two Melbourne hospitals. Eighteen had a dominant epileptogenic zone (EZ) (temporal=10, frontal=4, insula=2, nodular heterotopia (NH)=2), 16 a non-dominant EZ (temporal=11, frontal=2, insula-2, NH=2, hypothalamic haematoma=1), and 4 a bilateral EZ (bitemporal=3, bilateral NH=1). All patients underwent RF-THC with a mean of 11.58 (*SD*=7.73) coagulation sites. A comprehensive neuropsychological assessment was administered before implantation and 3-months after RF-THC (*M*=108.11 days, *SD*=28.67). Outcomes across cognitive domains were assessed at a group level with repeated measures t-tests. Repeated measures ANOVAs compared memory and language outcomes according to whether dominant mesial temporal lobe (mTL) structures were coagulated. Reliable change indices were undertaken to explore clinically meaningful changes at an individual level.

Results: At a group level, RF-THC was not associated with a decline in any cognitive domain. Subgroup analysis revealed a decline in verbal memory following RF-THC of dominant mTL structures, $F(1,36)=4.85$, $p=.03$. No significant differences in visual memory, $F(1,34)=2.24$, $p=.67$ or confrontation naming $F(1,34)=3.14$, $p=.09$ were observed. Reliable change indices revealed while overall 63% of patients experienced an improvement on a cognitive task, 20% experienced a decline on a measure of executive functioning, 16% visual memory, 14% verbal memory, 14% confrontation naming, 13% processing speed and 7% attention.
Conclusion: RF-THC of dominant mTL structures is associated with a decline in verbal memory at three months. Additionally, 55% of patients experienced a decline in at least one cognitive domain. These findings highlight that RF-THC may cause a decline in cognition and appropriate neuropsychological counselling is essential.

947

Developmental trajectories in developmental and epileptic encephalopathies

T Lo Barco[1,2], F Offredi[1,2], A Cossu[1,2], J Proietti[1,2], G Cantalupo[1,2], B Dalla Bernardina[2], F Darra[1,2]
[1]University of Verona, Child Neuropsychiatry, 37124, Italy, [2]Research Center for Pediatric Epilepsies, 37124, Italy

Purpose: Developmental and epileptic encephalopathies (DEEs) are rare disorders where neurodevelopmental impairment is caused by an underlying cause and worsened by uncontrolled seizure activity. It is a heterogeneous group with wide variability of cognitive disability and impaired functioning. With the aim to explore this diversity, we analyzed the neurodevelopmental trajectories of patients affected by genetic DEEs followed at our centre.
Method: We included in the study individuals with a genetic DEE, diagnosed accordingly with the ILAE definition, and having tested at least once with standardized cognitive quotient (IQ) or developmental quotient (DQ) scales. We then analyzed the distribution of the developmental/cognitive scores at three time points: 0-3 years (T0), 6-10 years (T1), 11-15 years (T2).
Results: 168 patients were enrolled with 22 different types of DEE, including Dravet Syndrome (n=50), TSC1/2 (n=24), Angelman Syndrome (n=15), PCDH19 (n=14), CDKL5 (n=12), KCNQ2 (n=7), SLC2A1 (n=7), GRIN2A (n=5), and others.
Age at developmental/cognitive evaluation ranged from 4 months to 26 years.
137 patients were tested repeatedly, and 69 subjects were tested at T0 and T1 and/or T2.
At T0, neurodevelopment was normal in 69%, mildly impaired in 9%, moderately impaired in 7%, severely impaired in 15%.
At T1 (n=62), IQ was normal in 31%, mildly impaired in 31%, moderately impaired in 13%, severely impaired in 25%.
At T2 (n=43), only 9% obtained a normal IQ; a mild cognitive impairment was seen in 12%, and remaining patients had a moderate (16%) or severe impairment (63%).
Conclusion: Repetition over time of the cognitive assessment is essential in the care of patients with DEEs in terms of therapeutic decisions and rehabilitation planning. They also allow to identify diverse neurodevelopmental trajectories between the different types of DEEs, with major implications in terms of outcome definition. Anyway, a “floor effect” becomes evident

with advancing age, highlighting the need for disease-specific severity measures.

1126

Abnormal metabolic patterns revealed by ^{1}H MR spectroscopy associate with cognitive findings in progressive myoclonus type 1 (EPM1) patients

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Purpose: Patients with progressive myoclonus epilepsy type 1 (EPM1) show severe progressive myoclonus, which is associated with impairment in psychomotor speed and executive function cognitive domains. Patients' verbal memory is usually largely preserved. Previous MRI studies showed gray matter volume loss in sensorimotor and supplementary motor areas and thalamus. The aim of this study was to examine metabolic changes in EPM1 patients using MR spectroscopy (MRS).
Method: Eighteen EPM1 patients (9M, 9F) underwent clinical evaluation and neuropsychological testing, which included assessment of intellectual ability, verbal memory, and psychomotor and executive functions. The imaging studies were conducted with a 1,5T MRI system. 2D Chemical Shift Imaging (CSI) spectral maps (TE=135) were obtained for the following regions of the brain: basal ganglia, thalamus, insula, splenium and occipital white and grey matter. N-acetyl-aspartate (NAA)-, choline (Cho)- and lactate (Lac)-to-creatine (Cr) ratios were analyzed. Ten healthy subjects (5M, 5F) were used as controls for MRS.
Results: Thalamic, splenium and occipital white matter Lac/Cr was increased, and basal ganglia and insular NAA/Cr was decreased in EPM1 patients compared to healthy controls. Cho/Cr changes in white matter were associated with myoclonus severity (r^2 0.682, p=0.002). Verbal IQ and Performance IQ correlated significantly negatively with Cho/Cr, NAA/Cr and Lac/Cr in the right insula. Basal ganglia and thalamic Cho/Cr and NAA/Cr correlated with the results of verbal memory tasks. In comparison, complex psychomotor and executive function tests' results were associated with Lac/Cr changes in basal ganglia, insula, thalamus and white matter.
Conclusion: We found wide range of metabolic changes in basal ganglia, thalamic nuclei, insula, and occipital areas of EPM1 patients. Different metabolite changes especially in the right insula, basal ganglia and thalamus were associated with global cognitive abilities and impairment of psychomotor and executive functions of EPM1 patients. Multiple widespread metabolite changes support the presence of neurodegeneration associated with EPM1 progression.

1262

Prevalence and risk factors for anxiety and depression in adult patients with epilep-

sy: a multicenter survey-based study

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Purpose: The study was undertaken to evaluate the prevalence and risk factors of anxiety and depression among Chinese adult patients with epilepsy (PWE).
Method: Adult PWE were recruited from thirteen tertiary epilepsy centers from February to September 2022. Generalized Anxiety Disorder-7 (GAD-7) and Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) were applied to evaluate anxiety and depression, respectively. Both univariate and multivariate logistic regression were performed to explore risk factors of anxiety and depression.
Results: A total of 1326 PWE were enrolled in this study, 691 (52.1%) were males. The median age of participants was 32 years. The prevalence of anxiety and depression were 31.45% and 27.30%, respectively. Being female (OR = 1.465, 95%CI: 1.133-1.897, *P* = 0.004), having two epilepsy types (refers as focal and generalized epilepsy) (OR = 1.396, 95%CI: 1.019-1.906, *P* = 0.036) and seizure occurrence in the last 3 months (OR = 1.445, 95%CI: 1.026-2.044, *P* = 0.036) were risk factors for anxiety. Having two epilepsy types (OR = 1.523, 95%CI: 1.096-2.107, *P* = 0.012) and seizure occurrence in the last 3 months (OR = 1.643, 95%CI: 1.130-2.410, *P* = 0.010) were risk factors for depression. In addition, for every 1-year increment of age, the odds of developing depression were decreased by 3.8% ($P = 4.07e^{-5}$). Nevertheless, there was up to 70% PWE did not receive any anticomorbidity treatment.
Conclusion: There was approximately 30% PWE suffered from anxiety or depression. Both having two epilepsy types and seizure occurrence in the last 3 months were demonstrated as risk factors for anxiety and depression. However, the current status of treatment was not optimistic. Clinicians should pay attention to screening and management for psychiatric comorbidities in clinical practice.

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The wellbeing neuro course: a randomized controlled trial of an internet-delivered transdiagnostic psychological intervention for adults with epilepsy and other neurological disorders

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Purpose: Mental health and functional difficulties are highly comorbid in people with epilepsy and other neurological disorders. However, accessible psychological care options in neurology are limited.
Method: This Randomized Controlled Trial assessed the efficacy of a novel transdiagnostic internet-delivered psychological intervention in 215 (treatment n = 111; control n = 104). adults with a confirmed diagnosis of epilepsy (n = 34), multiple sclerosis (n= 85), Parkinson's disease

(n = 43), or an acquired brain injury (n = 53). The intervention, the Wellbeing Neuro Course, includes six lessons, based on principles of Cognitive Behavioral Therapy (CBT) and Compensatory Cognitive Rehabilitation, delivered over 10-weeks with support from a psychologist via email and telephone.
Results: At post-treatment, we observed overall significant between-group differences on our primary outcomes of depression (PHQ-9; hedges g = 0·62), anxiety (GAD-7; g = 0·41) and disability (WHODAS 2.0; g = 0·31), that favoured treatment (all ps < 0·001). We also observed overall significant between-group differences on secondary outcomes of cognitive function (Neuro-Qol; g = 0.37), emotional/behavioral dysycontrol (Neuro-Qol; g = 0.45) and cognitive strategy use (CCSQ; g = 0.41), favoring treatment (ps < 0·001). Treatment-related effects maintained at 3-month follow-up. For the epilepsy subsample, there were significant group-differences for depression (p = .006) and anxiety (p = .07) but not for disability (p = .112). However significant improvements in disability from pre-treatment to 3-month follow-up emerged (p = .019). Findings were achieved with modest clinician time (average of 95·7 min [SD = 59·3]) per participant.
Conclusion: A carefully designed remote psychological intervention based on modified CBT was highly acceptable and efficacious for adults with a range of neurological disorders, including epilepsy.

Paediatric Epileptology

15:30 - 16:30
Sunday, 3 September
Auditorium

1025

Contralesional epileptiform activity in Rasmussen's Encephalitis is associated with early disease onset, cortical and microstructural alterations in the contralateral hemisphere, cognitive decline, and unfavorable outcome after hemispherotomy

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Purpose: To quantify contralesional epileptiform activity (CEA) in Rasmussen's encephalitis (RE) and uncover its functional and structural underpinnings.

Method: Individuals with RE treated at the University Hospital Bonn between 2000 and 2018 (n=68, 39 females, median onset 7 years), were retrospectively ascertained. All available EEGs (N=531) were reviewed, and interrater reliability was assessed in a randomly chosen subset (N=273). The temporal occurrence of CEA (interictal discharges or seizure onset) was assessed using mixed-effects logistic regression. Cases with CEA were compared to cases without CEA regarding neuropsychological impairment, inflammation (histopathological markers from ipsilesional brain biopsies), cortical morphometry (FreeSurfer) and white matter microstructure (fixel-based analysis). EEG findings were validated on a second cohort treated at the Great Ormond Street Hospital for Children, London between 1995 and 2020 (n=59, 35 females, median onset 6 years, N=156 EEGs).
Results: CEA was observed preoperatively in 30/68 (44%) in Bonn (κ=0.39), and 8/59 (14%) in London. Across both cohorts, occurrence of CEA was associated with younger age at onset (OR 0.9, 95%-CI [0.83, 0.97], P=0.006). In Bonn, CEA was associated with contralesional morphometric alterations in the temporoparietal junction, postcentral gyrus, temporal pole, and insular cortex (FWE-corrected P<0.05), lower fiber density and cross-section of contralesional white matter tracts (P<0.05), as well as with lower intelligence (OR 5.19, 95%-CI [1.28, 21.08], P=0.021) and impaired verbal memory (OR 10.29, 95%-CI [1.97, 53.85], P=0.006). In Bonn, 11/17 (65%) and in London, 28/37 (76%) were seizure-free after hemispherotomy. In Bonn, contralesional epileptiform activity was persistent postoperatively in 6/12 (50%), in London in 2/34 (6%). Across both cohorts, preoperative contralesional epileptiform activity reduced the chance of postoperative seizure freedom (OR 0.69, 95%-CI [0.50, 0.95], P=0.029).
Conclusion: Our findings question the concept of a strict unilaterality of RE and provide evidence of CEA as a possible EEG predictor of unfavorable postoperative seizure outcome.

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Quantitative MRI correlates of epilepsy and cognitive deficits in school-age children and young adults with Sturge-Weber syndrome

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Purpose: Early seizure onset and uncontrolled seizures are major risk factors of poor neurocognitive outcome in young patients with Sturge-Weber syndrome (SWS). While anti-seizure medication can result in reasonable seizure control and help avoid epilepsy surgery, many patients show cognitive deficits and brain atrophy in the affected hemisphere. In this prospective study we evaluated hemispheric volume and cortical surface area abnormalities and their association with seizure and cognitive variables in school-age children and young adults with SWS and their healthy siblings.
Method: Eighteen subjects (age 7-24 years, mean: 15 years), including 9 patients with unilateral SWS with a long history (6-23 years) of epilepsy but low seizure frequency (up to a few/year), and 9 healthy control siblings, underwent high-resolution 3T MRI and neurocognitive

testing prospectively. Using volumetric T1-weighted images, hemispheric white matter volume and cortical surface area were quantified, and severity of atrophy in the SWS group was characterized by their affected/unaffected hemispheric ratios. MRI and clinical variables were correlated using Spearman's rank correlations.
Results: Hemispheric white matter volumes and cortical surface areas in the unaffected hemispheres of SWS patients were similar to those of their healthy siblings. White matter volumes increased with age in the unaffected but not in SWS-affected hemispheres. Longer epilepsy duration was associated with lower affected/unaffected hemispheric ratios of white matter volume (r=-0.73, p=0.028) and cortical surface area (r=-0.65, p=0.058). SWS patients showed mild-moderate cognitive deficits (mean full-scale IQ: 84; range: 66-97). Lower white matter volume in the SWS-affected hemispheres was associated with lower non-dominant hemispheric cognitive functions (r=0.70, p=0.036).
Conclusion: In school-age children and young adults with unilateral SWS, longer disease duration is associated with a greater gap of white matter volumes and cortical surface area between affected and unaffected hemispheres. Low white matter volume in the affected hemisphere may account for some of the long-term cognitive deficits.

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The ENVISION study, an international, prospective natural history study in young children with *SCN1A*+ Dravet syndrome, 18-month follow-up

S Boronat[1], MS Perry[2], IE Scheffer[3], J Sullivan[4], J Wheless[5], A Brunklaus[6], L Laux[7], A Patel[8], C Roberts[9], D Dlugos[10], D Holder[11], K Knupp[12], M Lallas[13], S Phillips[14], E Segal[15], D Lal[16], E Wirrell[17], S Zuberi[6], S Christensen[18], J Gofshteyn[18], N Huang[18], E James[18], MC Vila[18], S Rico[18] [1]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [2]Cook Children's Medical Center, Fort Worth, United States, [3]University of Melbourne, Austin Health, Melbourne, Australia, [4]University of California at San Francisco, San Francisco, United States, [5]Le Bonheur Children's Hospital, Memphis, United States, [6]Royal Hospital for Children, Glasgow, United Kingdom, [7]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, United States, [8]Nationwide Children's Hospital, Columbus, United States, [9]Doernbecher Children's Hospital, Portland, United States, [10]Children's Hospital of Philadelphia, Philadelphia, United States, [11]Children's Hospital Los Angeles, Los Angeles, United States, [12]Children's Hospital Colorado, Aurora, United States, [13]Nicklaus Children's Hospital, Miami, United States, [14]Multicare Health System, Tacoma, United States, [15]Northeast Regional Epilepsy Group, Hackensack, United States, [16]Cleveland Clinic Lerner Research Institute, Cleveland, United States, [17]Mayo Clinic, Rochester, United States, [18]Encoded Therapeutics, Inc., South San Francisco, United States

Purpose: Dravet Syndrome (DS) is a developmental and epileptic encephalopathy (DEE) with high seizure burden and many associated morbidities. There are limited prospective long-term data describing the evolution of symptoms with age. ENVISION is an observational study prospectively evaluating the course and impact of DS in young children and their families. Here, we will characterize impacts of DS in the first 1.5 years of ENVISION.

Method: Ongoing, international, longitudinal, prospective study of young children with *SCN1A*+ DS. Participants are assessed every 3 months for 24 months. Longitudinal progression of seizure burden, adaptive functioning, language, and cognitive functioning are evaluated using electronic seizure diary and validated tools (Bayley-III, Vineland-III, BRIEF-P).
Results: By 06Sep2022, 58 children were enrolled (median age 28 months). At enrolment 47% (27/58) of participants were <2 years. Median monthly countable seizure frequency (MCSF) increased with age, but high intraparticipant heterogeneity was observed (range 0–2549.3 seizures per 28 days at 3-month visit). Approximately 14–20% of the cohort had extreme seizure burden defined as MCSF ≥14.0 OR a requirement for rescue medication ≥4.0 times in a 28-day period. Cognition was universally impacted by age 2:3 years: months, with average BSID-III developmental quotient (DQ [±SD]) of 69.9% (±34.1). Language development was stagnated with average BSID-III language domain DQ of 57.7% (±29.6). Fourteen children had atypical language development patterns characterized by better expressive than receptive language skills. Executive functioning (BRIEF-P) showed marked deficits, particularly in domains of inhibitory self-control and metacognition. Predictive modelling indicated that developmental scores are independent of seizure burden.
Conclusion: Despite newer ASMs, participants have high seizure burden and early-onset of severe and persistent developmental stagnation. Global development stagnates by age 3 and is independent of seizures. Data from ENVISION indicate that a key therapeutic window for disease modifying therapy may exist prior to age 3 years.

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Establishing PROMs in medication management of rare genetic epilepsies: what are the best medications in 228 SYNGAP1 patients?

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Purpose: A major problem with rare diseases is that there is often little structured data on the efficacy of drugs, and it is often not known what the main goals and problems of drug therapy are. To solve these problems, we developed the data collection topics together with the patients' parents and collected drug efficacy data worldwide with them (PROMs - Patient Reported Outcome Measures). We started with one pilot disease, SYNGAP1-related developmental and epileptic encephalopathy (SYNGAP1).
Method: A multilingual online platform (based on REDCap) for patient collaboration and data collection was developed. In the survey, we asked parents' subjective evaluation of the medication. We worked out with the parents that in addition to the effect on seizures, the effects and side effects on behavior, development, and sleep are of very great interest in SYNGAP1.

Thus, the parents rated medications in these categories on a scale from -50/+50.
Results: We received 228 complete data sets from at least 15 countries, 20% of the known SYNGAP1-patients worldwide. We collected data on 49 medications. To motivate parents, we displayed the survey results immediately.
The best effects in the area of seizures were achieved by valproate, ethosuximide and clobazam, lamotrigine and CBD; In the behavioral area THC, statins and CBD; in the developmental area carbamazepine, statins and CBD and in the sleep area melatonin, THC, and clonidine.
Conclusion: Valproate, the most frequently used medication, and ethosuximide achieve a very good anticonvulsant effect, but have only a slight positive effect in the other three areas. Levetirazetam and perampanel had small positive effects on seizures, but such negative ratings on behavior, sleep, and development, that their use seems questionable.
Carbamazepine had unexpected ratings: on average, it worsened seizures, but there was improvement in development. We hope to elucidate this effect in the future through correlation with individual SYNGAP1-mutations.

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Ketogenic diet in infants with epilepsy (KIWE): a randomised controlled trial

N Schoeler[1,2], L Marston[3], L Lyons[3], S Halsall[3], R Jain[3], S Titre-Johnson[3], M Balogun[3], S Heales[2], S Eaton[4], M Orford[4], E Neal[4], C Eltze[2], E Stephen[5], A Mallick[6], F O'Callaghan[4], S Agrawal[7], A Parker[8], M Kirkpatrick[9], A Brunklaus[10], A McLellan[11], H McCullagh[12], R Samanta[13], R Kneen[14], J Tan[15], A Devlin[16], M Prasad[17], R Rattihalli[18], H Basu[19], A Desurkar[20], R Williams[21], P Fallon[22], I Nazareth[3], N Freemantle[3], JH Cross[1,2] [1]UCL Great Ormond Street Institute of Child Health, London, United Kingdom, [2]Great Ormond Street Hospital for Children, London, United Kingdom, [3]UCL, London, United Kingdom, [4]UCL Great Ormond Street Hospital for Children, London, United Kingdom, [5]Royal Aberdeen Children's Hospital, Aberdeen, United Kingdom, [6]Bristol Royal Hospital for Children, Bristol, United Kingdom, [7]Birmingham Children's Hospital, Birmingham, United Kingdom, [8]Cambridge University Hospitals, Cambridge, United Kingdom, [9]Tayside Children's Hospital, Dundee, United Kingdom, [10]Royal Hospital for Children, Glasgow, United Kingdom, [11]Royal Hospital for Sick Children, Edinburgh, United Kingdom, [12]Leeds Children's Hospital, Leeds, United Kingdom, [13]University Hospital of Leicester, Leicester, United Kingdom, [14]Alder Hey Children's Hospital, Liverpool, United Kingdom, [15]Royal Manchester Children's Hospital, Manchester, United Kingdom, [16]Great North Children's Hospital, Newcastle, United Kingdom, [17]Queens Medical Centre, Nottingham, United Kingdom, [18]Oxford University Hospitals, Oxford, United Kingdom, [19]Royal Preston Hospital, Preston, United Kingdom, [20]Sheffield Children's Hospital, Sheffield, United Kingdom, [21]Evelina London Children's Hospital, London, United Kingdom, [22]St George's Hospital, London, United Kingdom

Purpose: Many infancy-onset epilepsies are poorly responsive to anti-seizure medicines (ASMs) with poor prognosis for neurodevelopmental outcome. Ketogenic diets (KD) can reduce seizures in older children and adults. We aimed to assess the effectiveness of the KD in infants in a randomised controlled trial.
Method: Infants (age 1-24 months) with epilepsy, average ≥4 seizures/week and previous trial ≥2 ASMs, were randomised to receive a classical KD or further ASM. The primary outcome was difference in number of seizures during weeks 6-8 accounting for baseline.
Results: 78 children were randomised to KD and 58 to ASM. The median number of daily seizures was similar in both groups at 8 weeks (IRR 1.33 95% CI 0.84, 2.11). The odds ratio of achieving ≥50% seizure reduction was 1.21 (95% CI 0.55, 2.65), and 0.88 (0.27, 2.80) for seizure freedom. A higher proportion of infants in the ASM group changed the number or dose of concurrent ASMs during the intervention period (24/48 [50%]) compared to KD (9/66 [14%]). Side effect score at 8 weeks was similar in both groups (KD median 40 IQR 38,42; ASM 41 39,44). Overall health was numerically higher in the KD group (median 60 IQR 30, 60) at 8 weeks compared to ASM (median 30 IQR 30, 60).
Communication (2.79 95% CI -8.14, 13.72) and socialisation (1.12 95% CI -17.13, 19.36) numerically improved in the KD group compared to ASM at 12 months.
A similar proportion of infants in both groups reported at least one serious adverse event (43% ASM; 51% KD) - most commonly seizures.
Conclusion: KD appears numerically similar in efficacy and tolerability to further ASM in infants with drug-resistant epilepsy. The odds ratio of achieving seizure freedom at 8 weeks, and communication, socialisation and overall health scores numerically favoured KD compared to further ASM.

Social Issues/Nursing

15:30 - 16:30
Monday, 4 September
Liffey A
705

Adapting a self-management program for adolescents with epilepsy

R Fraser[1], E Johnson[1], E Novotny[2] [1]University of Washington, Department of Rehabilitation Medicine, Seattle, United States, [2]Seattle Children's Epilepsy Center, Seattle, United States

Purpose: The Program of Active Consumer Engagement in Self-management (PACES) in Epilepsy, an 8-session group program, was created and validated with adult patients based on multiple surveys, focus groups, and randomized controlled trials (RCT) (Fraser et al., Epilepsy and Behavior, 2011, 20, 291296). RCT data showed immediate and long-term effects on mood, epilepsy self-management and self-efficacy, and QoL (Johnson et al., Epilepsia, 2020,

61, 11291141). The objective was to devise and evaluate program efficacy of a new "Teen PACES" Epilepsy selfmanagement program.
Method: Focus group research to saturation was conducted, using a set question group with (a) adolescents with epilepsy age 14-15; (b) adolescents with epilepsy age 16-17; and (c) parents of adolescents aged 14-17 with epilepsy).
Results: Both teen groups indicated salient problems with seizure management and medication side effects. Adolescents aged 14-15 indicate problems with epilepsy disclosure; changes in activities and participation; experiencing bullying; psychosocial resources; and parental restrictions/hypervigilance. They preferred a peer-based group lead by a young adult epilepsy professional and trained peer which meets on multiple occasions through a medical establishment.
Adolescents age 16-17 indicate problems with driving and independence; the future (school, work, and relationships); epilepsy disclosure; changes in activities and participation; and parental restrictions/hypervigilance. They desire 1:1 self-management intervention with their doctor.
Parents report problems with vigilance, medication concerns/worry, restricting teen activities for safety, access to resources/teen isolation, and managing conflict with teens desiring independence.
Conclusion: This is a unique teen need effort. Program materials are being revised with more emphasis on youth-engaging, less densely presented material for several site RCTs.
This research effort is supported by the University of Washington Health Promotion Research Center cooperative agreement, Centers for Disease Control and Prevention, U.S.D.H H.S., award no. 5U48DP0063980400. The contents are those of the authors and do not represent endorsement by CDC/HHS.

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Pre-surgical preparation and post-surgery recovery: suggestions for patient-provider partnerships

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Purpose: In a province-wide study of people with epilepsy (PWE), the Ontario Health Technology Advisory Committee discovered that of 9,375 individuals who could benefit from epilepsy surgery, less than 2% of them obtained surgery due to the lack of a systemic approach to the problem. As a PWE who underwent successful epilepsy surgery and is actively involved in patient advisory committees, I will share my experience with pre-surgical decision-making, post-surgical recovery, and offer suggestions for a counselling program for surgical candidates to provide a proper understanding of surgery and recovery.
Method: The presentation will draw from my lived experience as a patient who underwent a left temporal lobectomy and amygdalohippocampectomy, as a peer-support worker for Epilepsy Toronto (2013-2020), and as a Research Coordinator for Dalhousie University's Department of Neuroscience. Secondary literature, and consultation with the Epilepsy Association of

the Maritimes and Dalhousie Medical School will supplement my discussion with a picture of the current treatment of epilepsy in Nova Scotia, Canada, and the challenges it faces.
Results: As a PWE who has worked as a member of the Patient Advisory Committee to the Centre for Addiction and Mental Health in quality improvement projects since 2020 and provides an alternative perspective to research teams at Dalhousie University in proposals and publications on the treatment of epilepsy, I will offer an alternative perspective on potential approaches to developing a pre-surgical complex intervention and guidelines for post-surgical recovery.
Conclusion: This presentation will provide clinicians and researchers a myriad of thoughts and suggestions from a PWE's perspective on ways to improve the number of candidates who choose to undergo epilepsy surgery. These include public preparation groups that blend former surgical patients and medical practitioners, vetted, informative resources for surgery candidates and/or their families, and emergency support for those in the final pre- or immediate post-surgery stage.

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Dance, equine-assisted therapy and social participation of people with epilepsy

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Purpose: Several neurological conditions are associated with epilepsy, and physical interventions are important for functioning and participation of people with epilepsy (PWE) (Duñabeitia et al., 2022). This study analyzed the influence of dance practice and equine-assisted therapy on functional independence, and social participation in PWE associated or not with other neurological conditions.
Method: PWE were randomly allocated to dance practice (DP) or equine-assisted therapy (EAT). Both interventions consisted of twenty-four sessions (one-hour, once a week). The EAT group used the horse as the main therapeutic resource with accessories such as ball, stick, types of ground, and different mounts (side, back, front). These activities always occurred outdoors. Each session was divided into approaching the horse and stimulating the touch; free riding and riding with activities, and route with variation in pace and terrain (Souza-Santos et al., 2018). The Dance group used theater rehearsal room. Dance classes were based on kinesthetic empathy (imitation by mirroring the qualities), body resonance (adjustment of two bodies moment-to-moment in a two-sided process), attunement (forms of intersubjectivity), synchrony (movement coordination between two or more individuals) (Teixeira-Machado et al., 2022). Pre- and post-interventions were conducted using the Functional Independence Measure (FIM) and World Health Organization Disability Assessment Schedule (WHODAS, 2.0 version) (Teixeira-Machado et al., 2017).
Results: Ninety-four participants, aged 17.40±4.65 years, 53.06% males were included in this study. Forty-five participants underwent DP group and forty-nine EAT group. Differences between the DP and EAT groups were significant at post-intervention for communication (mean

difference: 1.31; 99.8%CI: 0.29, 2.32, p < 0.001, d = 0.93) and social cognition (mean difference: 1.01; 99.8%CI: 0.13, 1.89, p < 0.001, d = 0.82). There were no significant between-group differences regarding social participation.
Conclusion: Contact and relationship with the horse, and corporal dialog during dancing are promising interventions for functioning and social participation of PWE.

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Improving acute seizure management through an interprofessional education program

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Purpose: Inpatient seizures pose a major challenge to care teams. Applying evidence-based practices is crucial to providing high-quality and efficient care when managing seizures. Unfortunately, the lack of uniform practice among care team members often leads to adverse outcomes. The purpose of our study is to implement an interprofessional training program to standardize the approach to the acute management of seizures.
Method: Physicians and nurses from both adult and pediatric departments completed an e-learning module with lectures and were provided with badge flowcharts with a standardized seizure management algorithm and checklist. Electronic medical record data collection tools were utilized to record key metrics of seizure care such as time between seizure recognition and medication ordering verification, and administration, as well as patient hospitalization outcomes.
Results: Mean time of clinical event to administration was 15 minutes (SD = 24.6) for first line antiseizure medications and 25 minutes (SD = 60.8) for second-line therapies. Upon completion of the e-learning module, survey respondents who felt highly comfortable with recognizing seizures increased from 39 percent to 65 percent, and those who felt highly comfortable with managing seizures increased from 40 percent to 68 percent. Data collection for administration response times after completing the education module is ongoing.
Conclusion: Our post-implementation data shows that learners who participate in our program demonstrate increased confidence and knowledge about seizures. Therefore, we conclude that an education program aimed at improving inpatient acute seizure management is feasible, its impacts quantifiable, and could result in improved quality of care. In the future, the impact of online seizure management education programs can be quantified further by measuring improvements in time between seizure recognition and first- and second line antiseizure medication administration.

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Single centre evaluation of a consultant nurse led, 'One-Stop', First Seizure Clinic (FSC)

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Purpose: To evaluate a novel service designed to reduce waiting times and holistically evaluate people experiencing a suspected first seizure.
Method: A consultant nurse for the epilepsies (CN) triages ED referrals, replacing ED direct booking. Patients are allocated to one of two, weekly, FSCs. One is led by a consultant neurologist, the other by the CN. Patients receive an EEG and sometimes MRI at the FSC. Neurological examinations are provided by a senior clinical fellow.
Data collection utilises EpiNet, a comprehensive clinical recording system also used for research and audit.
Results: 91 patients were offered an appointment in the FSC; 89% attendance. 51% offered an appointment within two weeks of index seizure, 71% within a month. 72% of referrals were appropriate for FSC. 89% had EEG at or prior to the clinic; 73% non-contributary, 21% non-specific abnormalities, 7% epileptiform. No neurological examination findings relevant to epilepsy. 39% MRI at or prior to clinic, 51% afterwards; 72% normal, 21% involutional change or stroke, 7% incidental abnormality. 88% received a diagnosis; 19% unprovoked first seizure, 11% provoked first seizure, 11% focal epilepsy, 5% IGE, 7% epilepsy - unknown onset. 14% had NEAD (one NEAD/epilepsy). 27% received 1st antiseizure medication. 65% had epilepsy nurse follow-up. One required neurologist follow-up. 8% with a first provoked seizure were given patient-initiated follow-up, others discharged. At the EEC there will be additional data, including 12-month patient outcomes following treatment and review.
Conclusion: Patients with suspected first seizure must be seen rapidly by a clinician with expertise in epilepsy. Experienced, expert level, epilepsy nurses can safely lead FSCs. A 'one-stop' approach reduces hospital visits. Advice, crucially on safety, can be given at the time of diagnosis, with timely planned follow-up and access to the urgent helpline and clinics. The FSC provides opportunity for research, with an AI-based study planned.

Status Epilepticus
15:30 - 16:30
Tuesday, 5 September
Liffey A

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Cytokines in patients with new-onset refractory status epilepticus (NORSE) predict outcomes

A Hanin[1,2,3], J Cespedes[1,4], K Dorgham[5], Y Pulluru[1,6], M Gopaul[1], G Gorochov[5], DA Hafler[1], V Navarro[2,3], N Gaspard[1,7], LJ Hirsch[1] [1]Yale University School of Medicine, Neurology, New Haven, United States, [2]Institut du Cerveau ICM, Paris, France, [3]Hôpital Pitié-Salpêtrière, Neurologie, Paris, France, [4]Universidad Autonoma de Centro America, School of Medicine, San Jose, Costa Rica, [5]Sorbonne Université, Hôpital Pitié-Salpêtrière, Centre d'Immunologie et des Maladies Infectieuses, Paris, France, [6]Nebraska Medical Center, Omaha, United States, [7]Université Libre de Bruxelles, Brussels, Belgium

Purpose: To investigate inflammation using cerebrospinal fluid (CSF) and serum cytokines/chemokines in patients with New-Onset Refractory Status Epilepticus (NORSE) to better understand the pathophysiology of NORSE and consequences.
Method: Patients with NORSE (n=61, including n=51 cryptogenic), including its subtype with prior fever known as FIRES (febrile infection-related epilepsy syndrome), were compared to patients with other refractory SE (RSE, n=37), and control patients without SE (n=52). We measured 12 cytokines/chemokines in serum or CSF samples using multiplexed fluorescent bead-based immunoassay detection. Cytokine levels were compared between patients with and without SE and between the 51 patients with cryptogenic NORSE (cNORSE) and the 47 patients with a known-etiology RSE (NORSE n=10, other RSE n=37), and correlated with outcomes.
Results: A significant increase of IL-6, TNF-a, CXCL8/IL-8, CCL2, MIP-1a and IL-12p70 pro-inflammatory cytokines/chemokines was observed in SE patients compared to patients without SE, in serum and CSF. Serum innate immunity pro-inflammatory cytokines/chemokines (CXCL8, CCL2, MIP-1a) were significantly higher in patients with cNORSE compared to non-cryptogenic RSE. NORSE patients with elevated innate immunity serum and CSF cytokine/chemokine levels had worse outcomes at discharge and several months after SE ended.
Conclusion: We identified significant differences in innate immunity serum and CSF cytokine/chemokine profiles between patients with cNORSE and non-cryptogenic RSE. The elevation of innate immunity pro-inflammatory cytokines in patients with NORSE correlated with worse short- and long-term outcomes. These findings highlight the involvement of innate immunity-related inflammation, and possibly of neutrophil-related immunity, in cNORSE pathogenesis and suggest the importance of utilizing specific anti-inflammatory interventions in cNORSE.

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Mortality and risk of epilepsy after acute symptomatic status epilepticus following ischemic stroke and an updated prognostic model (SeLECT 2.0)

L Sinka[1], L Abraira[2], LL Imbach[3], D Zieglgänsberger[4], E Santamarina[2], J Álvarez-Sabín[2], C Ferrei-

ra-Atuesta[5], M Katan[6], N Scherrer[1], G Bicciato[1], R Terziev[1], C Simmen[1], KM Schubert[1], A Elshahabi[1], CR R Baumann[1], N Döhler[4], B Erdélyi-Canavese[4], A Felbecker[4], P Siebel[4], M Winklehner[7], TJ von Oertzen[7], J N. Wagner[7], GL Gigli[8], A Serafini[8], A Nilo[8], F Janes[8], G Merlino[8], M Valente[8], MP Zafra-Sierra[9], H Bayona-Ortiz[9], J Conrad[10], S Evers[10], P Lochner[11], F Roell[11], F Brigo[12], C Bentes[13], AR Peralta[13], T Pinho e Melo[13], MR Keezer[14], JS Duncan[15], JW Sander[15], B Tettenborn[4], MJ Koepp[15], M Galovic[1] [1]University Hospital and University of Zurich, Department of Neurology, Clinical Neuroscience Center, Zurich, Switzerland, [2]Vall d'Hebron Hospital Universitari, Barcelona; Universitat Autonoma de Barcelona, Epilepsy Unit, Department of Neurology, Barcelona, Spain, [3]Swiss Epilepsy Center, Klinik Lengg, Zurich, Switzerland, [4]Department of Neurology, Kantonsspital St. Gallen, St Gallen, Switzerland, [5]Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, United States, [6]Department of Neurology, University Hospital and University of Basel, Basel, Switzerland, [7]Kepler Universitätsklinikum, Department of Neurology 1, Neuromed Campus, Linz, Austria, [8]Department of Medicine, University of Udine and Clinical Neurology, Udine University Hospital, Udine, Italy, [9]Department of Neurology, Fundación Santa Fe de Bogotá, Universidad de Los Andes, Universidad del Bosque, Bogotá, Colombia, [10]Department of Neurology, University of Muenster, Muenster, Germany, [11]Department of Neurology, Saarland University Medical Center, Homburg, Germany, [12]Department of Neurology, Hospital of Merano (SABES-ASDAA), Merano-Meran, Italy, [13]Department of Neurosciences and Mental Health (Neurology), Hospital de Santa Maria-CHLN, Centro de Estudos Egas Moniz, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal, [14]Stichting Epilepsie Instellingen Nederland –(SEIN), Heemstede, Netherlands, [15]Department of Clinical & Experimental Epilepsy, UCL Queen Square Institute of Neurology, London WC1N 3BG & Chalfont Centre for Epilepsy, London, United Kingdom

Purpose: Comparison of mortality and risk of epilepsy following different types of acute symptomatic seizures.
Method: **Derivation cohort** (n=4,552, 2,005 female; median age 73 years):
Nine international sub cohorts with neuroimaging-confirmed ischemic stroke, without a history of seizures, and participating in a registry assessing poststroke seizures incepted as part of the SeLECT study
Replication cohort (n=39, 24 female; median age 78 years):
Three separate cohorts with acute symptomatic status epilepticus (ASSE) following neuroimaging-confirmed ischemic stroke
For categorization into status epilepticus (SE) or short seizures (i.e. not fulfilling criteria for SE), the revised definition of the ILAE was used. SE was only diagnosed in cases with clinical signs suggestive of convulsive or non-convulsive SE.
Results: Acute symptomatic seizures (ASS) occurred in 226 (5%) individuals in the derivation cohort, of whom 8 (0.2%) presented with ASSE. ASSE was independently associated with increased mortality (aHR 12.7, 95% CI 3.0-52.7, p<0.001) and risk of poststroke epilepsy (PSE) (aHR 4.3, 95% CI 1.3-13.9, p=0.02).
10-year mortality was 79% in those with ASSE, compared to 30% in those with short ASS and 11% in those without seizures. The 10-year risk of epilepsy in stroke survivors with ASSE was 81%, compared to 40% in survivors with short ASS and 13% in survivors without seizures. The

10-year risk of mortality and epilepsy in the replication cohort was 76% and 88%, respectively. We updated a previously described prognostic model ($SeLECT_{2.0}$) with the type of ASS as a covariate. $SeLECT_{2.0}$ successfully captured cases at high risk of PSE.
Conclusion: Individuals with stroke and ASS presenting as SE have a higher mortality and risk of epilepsy compared to those with short ASS or no seizures. The $SeLECT_{2.0}$ prognostic model adequately reflects the risk of epilepsy in high-risk cases and may inform decisions on the continuation of antiseizure medication treatment and the methods and frequency of follow-up.

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Prediction of long-term epilepsy after new-onset status epilepticus

M Rodrigo-Gisbert[1], L Gómez-Dabó[1], M Quintana[2], D Campos-Fernández[2], S Lallana[2], E Fonseca[2], L Abraira[2], M Toledo[2], E Santamarina[2] [1]Hospital Universitari Vall d'Hebron, Department of Neurology, Barcelona, Spain, [2]Hospital Universitari Vall d'Hebron, Epilepsy Unit, Neurology Department, Barcelona, Spain

Purpose: Long-term consequences of status epilepticus (SE) include cognitive and behavioral impairment or the development of epilepsy. However, these aspects have not been systematically studied in clinical practice. We aimed to evaluate the development of epilepsy after new-onset status epilepticus (SE) and its potential associated factors, in acute symptomatic and cryptogenic aetiologies.
Method: The study data were obtained from a prospective registry of all SE episodes occurring in adult patients over 16 years who attended our tertiary center from February 2011 to April 2022. We selected those with no previous history of epilepsy. We excluded patients who meet criteria for epilepsy diagnosis on SE debut, such as remote and progressive symptomatic aetiologies.
Results: We included 230 patients with a median age was 65.9±16.9 years, 112 (48.7%) were women. 198 (86.1%) were acute symptomatic and 32 (13.9%) cryptogenic. 55 (23.9%) presented unprovoked seizures during a mean follow-up of 2.8 years. The presence of non-convulsive SE in coma (p=0.014), first-line treatment time>1h (p=0.013), a cryptogenic aetiology (p=0.014), LPD pattern in EEG (p=0.002), EMSE scale (p=0.025), SE duration (p=0.045) and a super-refractory SE (p=0.007) were associated with a greater risk of post-SE seizure recurrence. After adjusting for identifiable confounders, a treatment delay>1h (p=0.027; HR 2.21, 95%CI 1.1-4.47), a cryptogenic etiology (p=0.034; HR 2.1, 95%CI 1.06-4.13), a super-refractory SE (p=0.017; HR 2.49, 95%CI 1.18-5.25), and LPD pattern (p=0.043; HR 1.82, 95%CI 1.02-3.23) emerged as independent predictors of subsequent epilepsy. Based on these findings, we designed the AFTER scale including Aetiology, First-line Treatment timing, EEG pattern, and super-Refractoriness (scoring 1 point for each item).
Conclusion: A cryptogenic aetiology, a delay in SE treatment initiation, super-refractoriness and the EEG pattern were associated with the development of long-term epilepsy. An appropriate early treatment is mandatory to avoid post-SE epilepsy in acute symptomatic and cryptogenic aetiologies.

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Machine learning prediction of seizure recurrence after status epilepticus

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Purpose: Tools to predict seizure recurrence after Status Epilepticus (SE) are lacking. Machine Learning (ML) is the artificial intelligence application providing systems the capability to learn from experience without being explicitly programmed. In this study, we explored the ability of ML models to predict seizure recurrence after SE.
Method: SE patients aged ≥16 years without previous history of seizures admitted to Vall d'Hebron University Hospital (Barcelona, Spain) from 2011 to 2021 were reviewed. Different Machine Learning techniques (k-NN, Naïve Bayes, Artificial Neural Networks, Support Vector Machines, Decision Trees, Random Forests) and the classic Logistic Regression (LR) model were applied to develop one- and two-year predictive models of seizure recurrence. 70% of the total sample was randomly selected to train the models; the remaining 30% was used for validation. The area under receiver operating curves (AUROC) with 95% confidence interval (95%CI) were performed to assess their predictive capability.
Results: 268 patients were included, of which 73 (27.2%) and 88 (32.8%) had seizure recurrence within one and two years, respectively. Factors significantly associated with two-year seizure recurrence were progressive symptomatic SE etiology ($p<0.001$), EEG pattern ($p=0.047$), and time to SE treatment >1.5 hours ($p=0.001$). Among ML techniques, all were superior to the LR model in predicting two-year seizure recurrence (overall accuracy >70%, compared to 67.2% in the LR model). K-NN (AUROC 0.801, 95%CI = 0.687–0.915), Support Vector Machines (AUROC 0.803, 95%CI = 0.693–0.914), Random Forests (AUROC 0.822 (95%CI = 0.709–0.935) algorithms proved the best predictive ability in the validation dataset, showing a better performance than the LR model (AUROC 0.738, 95%CI = 0.618–0.858). No ML technique was superior to LR in predicting one-year seizure recurrence.
Conclusion: In our study, ML techniques were superior to the LR model in predicting two-year seizure recurrence after SE in adults without previous history of seizures.

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Changes in synaptic dynamics underlies benzodiazepine resistance in paediatric status epilepticus

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Purpose: Over a third of children in status epilepticus (SE) do not respond to first-line treatment with benzodiazepines. Experimental data from animal models has suggested that dynamic changes in fast synaptic inhibitory signalling may lead to benzodiazepine resistance. However, it is unknown whether these synaptic mechanisms are indeed relevant in paediatric patients. Here we utilise EEG recordings as a clinically accessible insight into pathological brain dynamics that occur during SE. Through dynamic causal modelling (DCM) we then infer excitatory-inhibitory coupling parameters of cortical microcircuits in different brain states.
Method: We use DCM to test key hypotheses regarding benzodiazepine effects directly on EEG data recorded in patients during SE: (1) that benzodiazepines modulate inhibitory coupling in SE, (2) that there are differences in the balance of excitatory-inhibitory coupling in benzodiazepine responder's vs non-responders. We investigated a cohort of 26 paediatric patients (8 benzodiazepine responders) who were managed at the University Children's Hospital Zürich for SE. Using the DCM framework, we fitted hierarchical neural mass models to (1) identify which synaptic parameters best explain the observed EEG changes, and (2) infer group differences in synaptic parameters between responders and non-responders.
Results: The fitted DCMs captured the following changes in EEG broadband spectra associated with benzodiazepine treatment: (1) the observed changes across conditions were best explained through alterations in inhibitory coupling; (2) responders and non-responders differed in the modulation of inhibitory synaptic connections in the neural mass model.
Conclusion: Overall, this study demonstrates that the effect of benzodiazepines on macroscopic brain dynamics in paediatric patients with SE is best explained by dynamic shifts in inhibitory cortical synaptic signalling. The described group differences suggest that there may be baseline differences in cortical synaptic coupling which may be captured by DCM and used to help predict and optimise treatment responses in patients with paediatric SE.

Mixed Topics

15:30 - 16:30
Tuesday, 5 September
Liffey Hall 2

1011

Does maternal genetic liability to folate deficiency influence the risk of antiseizure medication-associated language impairment and autistic traits in children of women with epilepsy?

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Pharmacology, Bergen, Norway, [5]University of Bergen, Dept Clinical Science, Bergen, Norway, [6]Haukeland University Hospital, Dept Neurology, Bergen, Norway, [7]Oslo University Hospital, Dept Research and Innovation, Division of Clinical Neuroscience, Oslo, Norway, [8]Oslo University Hospital, National Center for Epilepsy, Oslo, Norway, [9]University of Oslo, Pharmacoepidemiology and Drug Safety Research Group, Dept of Pharmacy, Oslo, Norway

Purpose: To examine whether maternal genetic liability to folate deficiency interacts with antiseizure medication (ASM) exposure on the risk of language impairment and autistic traits in children of women with epilepsy.
Method: We included children of women with and without epilepsy with available genetic data enrolled in the Norwegian Mother, Father, and Child Cohort Study. Information on prenatal ASM exposure, maternal folic acid supplement use and dose, dietary folate, child autistic traits, and language impairment was obtained from parent-reported questionnaires during pregnancy and until the child was 8 years old. We examined the interaction between maternal genetic liability to folate deficiency expressed as either a polygenic risk score (PRS) of low folate concentrations or the maternal rs1801133 (CC or CT/TT) genotype in the methylenetetrahydrofolate reductase gene (the major genetic modifier of folate) and prenatal ASM exposure on risk of language impairment or autistic traits by using logistic regression models.
Results: We included 96 children of women with ASM-treated epilepsy, 131 children of women with ASM-untreated epilepsy, and 37 249 children of women without epilepsy. The PRS of low folate concentrations or maternal rs1801133 genotype did not interact with the ASM-associated risk of language impairment or autistic traits in ASM-exposed children compared to ASM-unexposed children. ASM-exposed children had increased risk of adverse neurodevelopment regardless of maternal rs1801133 genotype. In children of women without epilepsy aged 3 years, those with maternal rs1801133 CT/TT genotypes had increased risk of language impairment compared to those with maternal CC genotype (adjusted odds ratio 1.18, 95% confidence interval 1.05-1.34).
Conclusion: Neither maternal PRS of low folate concentrations nor the rs1801133 CT/TT genotype interacted with the ASM-associated risk of language impairment and autistic traits in ASM-exposed children. Widespread maternal use of folic acid supplements may counteract adverse effects of maternal genetic liability to folate deficiency in children of women with epilepsy.

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Visualizing the 2022 classification of epilepsy syndromes: an interactive teaching resource

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Neurology, Nancy, France, [4]Research Center for Automatic Control of Nancy (CRAN), Lorraine University, CNRS, Biologie, Signaux et Systèmes en Cancérologie et Neurosciences, Vandoeuvre, France, [5]University of Bologna, Department of Biomedical and Neuromotor Sciences, Bologne, Italy, [6]Scientific Institute for Research and Health Care, Institute of Neurological Sciences, member of EpiCARE, Bologna, Italy, [7]University College London National Institute for Health Research Biomedical Research Centre Great Ormond Street Institute of Child Health, Great Ormond Street Hospital for Children, and Young Epilepsy Lingfield, Programme of Developmental Neurosciences, London, United Kingdom, [8]Mayo Clinic, Divisions of Child and Adolescent Neurology and Epilepsy, Department of Neurology, Rochester, United States

Purpose: Our proposed interactive tool aims to provide an educational tool for the classification of epilepsy syndromes. By using the guidelines from the ILAE working group in 2022, the tool provides a comprehensive visualization of the classification system, including the age of onset for each syndrome, different nosological groups, and access to important information such as mandatory electro-clinical criteria, warning points, and exclusion criteria for each syndrome.
Method: The development of this interactive tool involved the utilization of multiple software programs including R, Inkscape, GIMP, PowerPoint, and Visual Basic.
Results: We propose an updated diagram of epilepsy syndromes across age groups. First, we classified the epilepsy syndromes based on the type of epilepsy (focal seizure, generalized seizure and combining generalized and focal seizures, as per the ILAE 2017 classification). Then, using a logarithmic concentric scale, we illustrated the extreme and typical ages of onset for each syndrome, allowing us to include syndromes with adult onset. To visualize the different groups of epilepsy syndromes, we grouped them with specific colors. In addition, the diagram is divided into two sections, with self-limited or classically pharmaco-sensive epilepsy on one side and pharmaco-resistant epilepsy on the other. Finally, we made this figure interactive by linking the different syndromes to the corresponding tables allowing to display for each syndrome its mandatory electro-clinical criteria, its warning points, which should prompt a reassessment of the criteria to confirm the syndrome, and its exclusion criteria, which would invalidate the diagnosis when they are present.
Conclusion: Understanding and classifying epileptic syndromes can be a challenging task, and we hope that this interactive tool will be a helpful resource for learning and applying these concepts in clinical practice.
PS: this work was accepted in Epilepsia open in October 2022

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Personalized therapeutic management of epilepsy patients with metabolic breath analysis

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Department of Biomedical Engineering, Basel, Switzerland

Purpose: Therapeutic management of epilepsy remains a challenge, since optimal systemic antiseizure medication (ASM) concentrations do not always correlate with improved clinical outcome and minimal side effects. A previous study (Singh KD et al. Commun Med 2021; 1:21.) tested real-time breath analysis as a novel method for therapeutic drug monitoring (TDM) in comparison to blood based TDM. The metabolome was assessed from 130 breath measurements of 91 pediatric and adult patients with epilepsy from two clinical centers with secondary electrospray ionization and high-resolution mass spectrometry (SESI-HRMS). The systemic concentration of the ASM valproic acid (VPA) could be estimated with a concordance of ≤0.63, with high inter and intra-patient variability in the VPA metabolism. Furthermore, patients suffering from side effects and non-responders showed changes in the metabolism of amino acids and tyrosine, respectively.
Method: The present study aims (i) to validate the results of the previous study in a larger cohort of adults, and (ii) to expand the method on other ASMs like levetiracetam and lamotrigine. Therefore, the breath metabolome of 300 epilepsy patients will be measured with SESI-HRMS. As in the previous study, we will also investigate if the occurrence of side effects and insufficient treatment response is associated with metabolic changes.
Results: Based on previous results, breath analysis can be used to non-invasively measure the concentration of VPA in epilepsy patients.
Conclusion: If these results can be expanded on additional ASMs, even more patients could benefit from this innovative and non-invasive method.

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Independent associations of incident epilepsy, enzyme-inducing, and non-enzyme-inducing antiseizure medications with the development of osteoporosis: a population-based analysis

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Purpose: Both epilepsy and enzyme-inducing antiseizure medications (eiASM) having varying reports of association with increased risks for osteoporosis. The purpose of this study was to quantify and model the independent hazards of epilepsy and ASMs for osteoporosis.
Method: Population-based linked primary care and hospital electronic health records cohort study that included all cases of incident adult-onset (≥18 years) epilepsy. Exposure to an eiASM was defined as those whose first four consecutive ASMs were for enzyme-inducers. The outcome was incident osteoporosis. Hazard was assessed using accelerated failure time models and incident epilepsy was treated as a time-varying covariate. All analyses controlled for age, sex, socioeconomic status, cancer, 1+ years of corticosteroid use, body mass index,

bariatric surgery, eating disorders, hyperthyroidism, inflammatory bowel disease, rheumatoid arthritis, smoking status, falls, fragility fractures, and osteoporosis screening tests. Additional analyses included propensity matching for receipt of an eiASM, restricted analyses to only those with incident onset epilepsy, and restricted analyses to the cohort of people that developed epilepsy at age ≥65.
Results: Of 8,095,441 adults, we identified 6,275 people with incident adult-onset epilepsy (incidence rate 62 per 100,000 person-years) with a median age of 56 (interquartile range 38-73) and 3,220 (51%) were female. When controlling for osteoporosis risk factors, incident epilepsy was independently associated with an increased risk for osteoporosis (time ratio [TR] 0.59, 95% confidence interval [95%CI] 0.52-0.67; p<0.001) as were eiASMs (TR 0.91, 95%CI 72 0.87-0.95; p<0.001) and non-eiASMs (TR 0.77, 95%CI 0.76-0.78; p<0.001). The independent associations between epilepsy, eiASMs, and non-eiASMs remained consistent in propensity matched analyses, cohorts restricted to adult-onset epilepsy, and cohorts restricted to late-onset epilepsy.
Conclusion: Epilepsy is independently associated with a clinically meaningful increase in the risk for osteoporosis, as are both eiASMs and non-eiASMs. Routine screening and prophylaxis should be considered in all people with epilepsy.

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Stimulation of the thalamus for arousal restoral in temporal lobe epilepsy (START) clinical trial

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Purpose: A primary goal of epilepsy treatment is to stop seizures; however, some seizures cannot be stopped, leading to impaired consciousness. Previous work suggests that impaired consciousness in temporal lobe seizures is related to depressed thalamocortical arousal. We aimed to restore arousal and consciousness in temporal lobe seizures through stimulation of the thalamic intralaminar central lateral nucleus (CL).
Method: Five patients with medically and surgically refractory temporal lobe epilepsy were

implanted in bilateral thalamic CL and in the hippocampi. Summit RC+S™ (investigational device donated by Medtronic) delivers responsive stimulation 1. to hippocampi for neuromodulation aimed at stopping seizures; and 2. to CL to improve ictal and postictal consciousness. Seizures trigger behavioral testing with an Automatic Response Testing in Epilepsy (ARTiE) watch.

Results: Baseline interictal ARTiE scores were near perfect (2.9 ± 0.2, N=5; maximum score 3.0). ARTiE scores were significantly decreased during seizures without CL stimulation ($p < 0.001$). We titrated CL stimulation parameters during non-seizure stages N2/N3 sleep. We found effective behavioral and electrophysiological arousal from sleep without side effects in all patients (N=5). The RC+S algorithm successfully provides responsive hippocampal stimulation for seizures. Only seizures that are not terminated within 5s then receive CL stimulation. The primary outcome is ARTiE behavioral score from the randomization phase, where each patient serves as their own control. Patients receive therapeutic or sham (0 mA) CL stimulation during each seizure, with double blinding to CL treatment type.

Conclusion: These results demonstrate the feasibility of sequential responsive stimulation of the hippocampus and thalamic CL. Automatic behavioral testing was impaired during seizures without CL stimulation. Stimulation of CL produced interictal arousal from stages N2/N3 sleep. Results of the randomization phase are pending at the time of abstract submission. If successful, we hope this new treatment approach will improve quality of life for people with medically and surgically refractory epilepsy.

In-Person Poster Presentations

Adult Epileptology

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SUDEP in New Zealand

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Purpose: To determine:

1. the incidence of SUDEP in New Zealand.
2. how this changes over time.
3. risk factors associated with SUDEP.

Method: All New Zealand coroners notify us of people with epilepsy (PWE) who die unexpectedly. Potential cases are also referred from other sources. Cases are assessed by two neurologists and a pathologist, according to the Devinsky criteria.
The study has been approved by the New Zealand Northern a Health and Disability Ethics Committee.
Results: The study commenced on 01/08/2019.
We were notified of 159 PWE who died suddenly during the first 2 years of the study.
We determined that:
85 patients died from Definite, Definite-plus, Probable or Probable Plus-SUDEP; (46 in year 1; 39 in year 2); 30 died from Possible SUDEP; 2 further patients died during their first seizure, but did not have a diagnosis of epilepsy; 40 had an alternative cause of death; the cause of death is still under review in 2 patients.
55 of 85 Definite or Probable SUDEP cases were male. 58% were aged between 20 and 50
New Zealand's estimated population at 30 June 2020 was 5,084,300.
This gives a crude incidence of SUDEP of at least 8.0/million of population per year. If possible, cases are included, then the rate of definite, probable and possible SUDEP is 10.3 / million per year
If the prevalence of epilepsy in New Zealand is 5.49 / 1000 people, then the incidence of SUDEP is between 1.52 / 1000 PWE and 2.06 / 1000 PWE (if possible cases are included.)
Conclusion: The estimated incidence of SUDEP for New Zealand is at least 8.0/million per year of population; this is significantly higher than determined by retrospective review. We are continuing to collect prospective data, to determine whether changes in epilepsy management reduce the rate of SUDEP.

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Clinical experience of treating highly refractory epilepsy patients with immunotherapy

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Purpose: To understand the clinical response of highly refractory epilepsy patients to immunotherapy and to establish a diagnostic and treatment pathway in the regional epilepsy service in Saint James Hospital, Dublin Ireland.
Method: Based on positive individual experiences in treating selected patients with highly refractory epilepsy patients in our service with immunotherapy as a palliative treatment trial we started to develop a structured approach to treating patients with Immunotherapy and develop a diagnostic pathway to seek out patient who might benefit from immunotherapy. Since 2018 we have investigated 61 Patients through our pathway for autoimmune epilepsy. The screening included assessment of clinical features, serum testing, cerebrospinal fluid testing, magnet resonance imaging, electroencephalogram and in selected female patients a pelvic imaging. Based on clinical features we treated 36 of these patients with immunotherapy.
Results: We found that the most helpful screening items were the evidence of highly frequent seizures with focal onset and an encephalopathic electroencephalogram with focal features. Serum and CSF testing for autoimmunity did not correlate significantly with treatment success in our cohort. Of the 36 patients that we treated with immunotherapy based on clinical features 3 patients became seizure free and 6 patients experienced a more than 50% reduction in seizure frequency. Some patients responded to single course of steroids while others have required continued immunotherapy to sustain the response. Based the treatment outcome of the patients treated to date (36 patients) we have developed a treatment algorithm for immunotherapy.
Conclusion: A third of this highly refractory cohort treated with immunotherapy have responded remarkably well to treatment with some patients becoming seizure free and others having a more that 50% improvement in seizure frequency. Further research is required to understand how and why patients respond to immunotherapy.

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Designing a palliative care program for selected epilepsy patients and their caregivers: a mixed methods study

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Purpose: Comprehensive care of persons with epilepsy (PWE) with global developmental delay, disability(s), progressive neurological disease and dependence for ADL on caregivers exceeds mere seizure control and management of conventional co-morbidities. Caregivers of such PWE too experience needs beyond the scope of care provided by contemporary models of care. This work attempts to design a palliative care (PC) program for such PWE and their caregivers.
Method: This is an ongoing mixed methods exploratory study. In the first step, a review of literature looked at PC program development and existing PC programs in neurological disorders. In the second step, an international, multi-specialty group of experts was constituted and presented with a list of PC domains that emerged from literature review as being relevant for PWE and their caregivers. Expert group consultations and consensus building using a Delphi process was conducted. Focus group discussions and a questionnaire-based survey are planned for PWE and caregivers.
Results: Thirteen experts voted on a total of 47 patient-related and 21 caregiver-related items under consideration for the PC program. These items were grouped under the domains: physical, social, psychological and spiritual. After two rounds of Delphi, a consensus with more than 75% agreement has been obtained on all but 5 items.
Conclusion: In this ongoing work, experts have proposed a palliative care program for PWE and their caregivers. Inputs from PWE and caregivers are still being collected. On completion of this work, we hope to present a comprehensive PC program for PWE and caregivers.

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Focal cortical notch lesions: a radiological biomarker complementing diagnostic criteria of late onset Rasmussen's encephalitis

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Purpose: Rasmussen's encephalitis is a rare, severe autoimmune disease starting generally during childhood. In adults, affected in 10%, diagnosis is more challenging because of a milder course. The main goal of this study was to carry out an in-depth morphological and longitudinal description of MRI of five patients with adult onset RE in order to delineate imaging biomarkers suitable to complement the diagnostic criteria of LRE.
Method: Here, we yield an in-depth longitudinal MRI-description of five patients with late onset Rasmussen's (LRE, 26 to 53 years). Diagnosis was based Bien's criteria (2005), for four of five confirmed by histology.
Results: The radiological evolution was less marked than in classical childhood cases. The first MRI regularly showed medial temporal inflammation. All patients then developed major atrophy centered on the initial focus but also encompassing the insula, parietal lobe and contralateral hemisphere, and the caudate nucleus in four of them.
A striking feature in the younger patients were hotspots of focal cortical moth-hole atrophy which we also found in three additional cases of childhood-onset LRE (9 – 15 years) with sometimes incomplete criteria. The two oldest patients (> 50 years), conversely, presented with atypical posterior lesions.
Conclusion: We propose that resilience to cortical destruction increases with age, leading to intermediate severity in late childhood and young adulthood, the hallmark of which are focal moth-hole lesions. These characteristic lesions could be a pertinent radiological biomarker in the challenge of refining diagnostic criteria in late onset Rasmussen's encephalitis.

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Prospective validation of a mobile and wearable app to forecast seizure risk

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Purpose: The unpredictability of seizures is debilitating and dangerous for people with epilepsy. Accurate seizure forecasters could improve quality of life but must be practical for long-term use. We recently launched a wearable and mobile app to forecast seizure risk using established cycles of seizure likelihood. Here we report on forecast performance and patient-reported outcomes.
Method: Two implementations of risk forecasts were validated and used during mobile app deployment: a diary-based forecast, using self-reported seizure times, and a diary+wearable forecast which also included signals recorded from a smartwatch.

Once the forecast app was launched, patient reported outcomes were assessed at different time points (5 months after launch, and 8 months after launch) with mood (NDDI-E) and anxiety (brEASI) surveys.
Results: During prospective, blinded validation, the diary-based and diary+wearable risk forecasters were assessed for 43 and 27 participants, respectively (mean test seizures: 135.8). Sixty-seven of 70 (95% of diary-based users and 96% of diary+wearable users) participants had forecasting performance above chance, with average sensitivities of 52% and 48%, and average specificities of 75% and 76%, respectively.
For both forecasting methods, higher accuracy was significantly correlated ($p<0.05$ using linear regression test) with longer recording durations, suggesting that forecast performance improves over time.
In the real world (unblinded) implementation, seizure risk forecasts were run continuously for 672 mobile app users over an 8-month period. Survey outcomes were collected for 101 users. Overall, 40% of users agreed risk forecasts were accurate enough to be useful (41% undecided, 18% disagreed). Users with higher anxiety were more likely to use risk forecasts.
Conclusion: This study represents the first prospective deployment of a non-invasive seizure forecast in a mobile application. Future work will initiate a prospective clinical trial to validate benefits of using a seizure risk app, such as improvements in anxiety or quality of life.

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Late-onset seizure after spontaneous intracerebral haemorrhage: a population-based retrospective cohort study

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Purpose: To identify the incidence and predisposing factors for late-onset seizure after spontaneous intracerebral haemorrhage (ICH).
Method: This retrospective cohort study enrolled 2,045 patients with spontaneous ICH between 2001 and 2013 from National Health Insurance Research Database of Taiwan. Patients who had trauma related diagnosis in the index hospitalization, other possible causes of late-onset seizure, including malignancy and ischemic stroke, or seizure before first ever ICH were excluded. A Cox proportional hazard model was used to estimate the association between eight risk factors and late-onset seizure. The difference of risk of late-onset seizure in treated and untreated subgroups of patients with hypertension was also compared by Cox model and Kaplan-Meier survival analysis.
Results: We identified 191 (9.3%) incident seizures among patients with spontaneous ICH in a median observation period of 3.1 years. Use of antiseizure medicine (aHR=0.1.49) and surgical management (aHR=2.74) associated with significantly higher risk of late-onset seizure, as ageing lower the risk slightly (aHR=0.986). Although hypertension only associated with

a non-significant reduction of late-onset seizure incidence in the initial study, further analysis showed that treated hypertension significantly decreased the risk of late-onset seizure (aHR=0.42) whilst untreated hypertension increased the risk significantly (aHR=3.53).
Conclusion: In our study, the incident rate of late-onset seizure after spontaneous ICH is 9.3%. Age, administration of antiseizure medication, surgical management and treatment of hypertension, not hypertension diagnosis itself, are closely tied to the occurrence of late-onset seizure after spontaneous ICH.

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Glioblastoma molecular correlates of seizure occurrence/recurrence after surgery: the role of p53 mutation

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Purpose: To identify molecular risk factors associated with seizure occurrence and/or recurrence after surgery in patients with brain glioblastoma.
Method: Patients with brain glioblastoma were consecutively enrolled and underwent brain surgery, followed by histopathological and molecular evaluation. Molecular (synaptophysin, GFAP, ATRX, p53, IDH, 1p/19q, ki67 index and MGMT gene promoter methylation) and clinical (age, sex and seizure occurrence/recurrence before and/or after surgery) data were collected. Molecular features were compared between patients with and without seizure occurrence/recurrence after surgery. A step-backward logistic regression was performed to investigate the association between molecular features and seizure occurrence/recurrence.
Results: 100 patients (age 59.51±1.23, 65 males) were enrolled. Forty-nine patients had seizures before surgery. After surgery, 40 patients (age 59.43±1.64, 27 males) had seizure occurrence/recurrence, while 60 (age 59.57±1.75, 38 males) had not. Patients with epilepsy (i.e., seizures before and/or after surgery) had lower synaptophysin (33.33%, p=0.008) and higher p53 (85%, p=0.038) mutation rate compared with patients without epilepsy. In the whole sample, seizure occurrence/recurrence after surgery was significantly associated with p53 mutation (OR: 3.9, CI 1.12-13.50, p=0.032) and seizure occurrence before surgery (OR: 5.3, CI 2.15-13.08, p<0.001). In patients without seizures before surgery, p53 mutation perfectly

predicted seizure occurrence, therefore the OR was not computable. In fact, all patients without p53 mutation didn't have seizure after surgery, while all patients that had seizure after surgery, also had p53 mutation (p=0.028). However, to note 71% patients with p53 mutation didn't have seizure after surgery.
Conclusion: The p53 mutation is related with a high risk of seizure occurrence/recurrence after surgery in brain glioblastoma, even in patients that didn't have seizures before surgery. Conversely, the absence of p53 mutation appears to protect against the occurrence of seizures. If confirmed, this result may help in the management of anti-seizure treatment after surgery in brain glioblastoma patients.

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The influence of nocturnal seizure on interictal cardiac and central autonomic alteration in frontal lobe epilepsy: heart rate variability and central autonomic network analysis

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Purpose: This study investigated the influence of nocturnal seizures on autonomic dysfunction in epilepsy.
Method: This retrospective study enrolled the frontal lobe epilepsy (FLE) patients, confirmed after 24-hr EEG monitoring. All participants were divided into diurnal FLE (DFLE) and nocturnal FLE (NFLE). The NFLE was defined as more than 90% of seizures occurring during sleep, and other participants were defined as the DFLE group. EEG and ECG signals were simultaneously obtained during each participant's sleep and wake stages, and EEG current density source and connectivity analysis of the autonomic network were performed. ECG was analyzed by time domain, frequency domain, and non-linear heart rate variability (HRV) analysis method. The EEG and HRV parameters were compared between NFLE and DFLE groups.
Results: Fifteen NFLE (12 males; mean age 24.0±9.0 years) and 16 DFLE (9 males; mean age 31.5±15.7 years) patients were involved. There was no significant difference in age, sex, disease duration, seizure frequency, and the number of antiepileptic drugs between the two groups. During the sleep stage, ECG analysis showed a significant decrease in HRV parameters in the NFLE group. In the sleep stage, NFLE group shows a significant increase of the beta-1 (13-22 Hz) current source density power (p<0.05) in the bilateral paracentral lobule (BA4,5,6) precuneus (BA7) and cingulate (BA31). NFLE group showed the central autonomic network hyperconnectivity (p<0.05, 12 edges distributed over 10 nodes), sympathetic hyperconnectivity (p<0.05, 2 edges distributed over 3 nodes), and parasympathetic hyperconnectivity (p<0.05, 4 edges distributed over 6 nodes) of the beta-1 frequency band during sleep. HRV and EEG analysis did not show significant differences during the wake stage.
Conclusion: Our result suggests that nocturnal seizure may be the most pronounced factor for interictal autonomic dysfunction during sleep. Frequent nocturnal seizures may be considered an important factor for autonomic dysfunction during sleep in epilepsy.

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Clinical perspectives on MOG mediated encephalitis and its role in anti-NMDAR encephalitis

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Purpose: Anti Myelin oligodendrocyte glycoprotein (MOG) antibodies have received an increasing attention on its role in autoimmune encephalitis and has also been detected in certain N-methyl-D-aspartate receptor encephalitis (NMDARe) patients. The first objective is to characterize MOG-antibody mediated autoimmune encephalitis as a rare subtype. The second is to investigate whether the clinical features are different between NMDARe and NMDARe with MOG-IgG tested positive later.
Method: We retrospectively analyzed the clinical features of twenty-two patients with MOG-IgG associated encephalitis. We also performed a comparative study of manifestation, auxiliary examination, and the number of relapses between NMDARe (group 1) and those tested positive for MOG-IgG later (group 2).
Results: MOG-antibody mediated encephalitis are predominantly characterized with seizure, abnormal behavior, cognitive and visual impairment. Patients in group 2 presented more prodromal headache (p=0.024), cognitive disorder (p=0.041), limbs weakness (p=0.005) and visual impairment ($p<0.001$). In the first brain MRI, lesions were found more often in corpus callosum (p=0.001), cingulate gyrus (p=0.008) and below the tentorium (p=0.012). Patients in group 2 had higher level of CSF protein than group 1 (p=0.02). Group 2 received more second-line immunotherapy ($p < 0.001$) and relapsed more frequently ($p < 0.001$).
Conclusion: MOG-antibody mediated encephalitis have some distinctive clinical features. Patients with MOG-IgG detected after NMDAR-IgG are easy to relapse, and different clinical features of the NMDARe patients with or without MOG-IgG assists clinicians in prognostic assessment.

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A call for better information about epilepsy: the next of kin perspective – an online survey

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Purpose: We have prior published that people with epilepsy (PWE) report insufficient information from health care workers concerning different aspects of their disease.
This study investigated whether Norwegian next of kin of PWE want information about different epilepsy-related issues and whether they actually obtain the information that they seek.
Method: We invited next of kin of PWE who visited the homepage of the Norwegian Epilepsy

Association to complete a web-based questionnaire about their perspective on obtaining information about epilepsy-related issues. The survey was accessible for a four-month period during 2017.
Results: More than 83% of the respondents (n = 231) wished general information about epilepsy, and over 85% wanted information on more specific issues like seizure types (90%), medication (90%), risk of seizure-related injuries (90%) and sudden death (87%). Issues like contraception (62%) and sexuality (75%) were less requested.
36% of the PWE report not having received any general information about the epilepsy of the patient.
Conclusion: For next of kin of PWE to have thorough knowledge of the disease is of crucial importance, both to cope with seizures, but also to convey the right attitudes towards the disease. Our survey shows that health care providers in Norway still have a way to go when it comes to communicating knowledge-based information to next of kin to PWE.

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Ketogenic diet as an underestimate resource for adults' drug resistant epilepsy

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Purpose: Ketogenic diet (KD) is considered a safe and effective dietary treatment for intractable epilepsy especially in children because of their better compliance and better and rapid efficacy. However, KD it is rarely proposed to adult persons with intractable epilepsy (PwIE) Aim: to assess efficacy and tolerability of KD in a retrospective cohort of PwIE including adolescents and adults, looking for strategies to increase its maintenance.
Method: A trained dietetic team and the referral epileptologist discussed each individual case and proposed a personalised classic KD regime, whose lipids to proteins ratio, on average, 2.3: 1 for adolescents and 2.5:1 for adults. Each diet was prescribed according to the clinical needs and the PwIE's personal attitudes. Furthermore, supplements of vitamins and oligo-elements were prescribed. Ambulatory blood tests (e.g. lipidic and protidic profile etc) and clinical assessment were performed on enrolllement and at 1, 3 , 6 ,12 months and home urinary ketons detection. Dietitian team and epileptologist offered additional email and phone consultation as required.
Results: Thirty-four PwIE were enrolled, of which seven adolescents (age [16, 17] years, mean age 16.5 years; mean diet duration 5.4 months) and 27 adults (age [18, 62] years, mean 33

years; mean diet duration: 9 months). KD was effective in sixteen adults (59.3%) and five adolescents (71.4%), as seizure reduction was >50%. The most common side effects reported were low energy, nausea, irritability and short-term memory and concentration impairments. Only one patient (2.9%) showed a significant alteration of the lipid profile requiring to interrupt the treatment.
Conclusion: Ketogenic diet may be a safe, effective and sustainable dietary treatment for patients with intractable epilepsy. An interdisciplinary assessment and care by a trained dietary team and the epileptologist may be a key factor for increasing the compliance of adult patients to this effective although underrated treatment option.

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Metrics for evaluation of seizure-onset zone localization

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Purpose: In focal drug-resistant epilepsy, precise localization of the epileptogenic zone is a requirement for successful surgical resection. Epileptogenic tissue can be localized using various machine learning models. However, clear guidelines for the evaluation of their performance are not established. We aim to test different classification metrics and recommend an approach suitable for objective model evaluation.
Method: Stereo-electroencephalography recordings from 18 patients with Engel-IA post-surgical outcomes were analyzed. Using a multi-feature approach, channels were classified by a support vector machine as normal or pathologic for three different classification targets (seizure-onset zone (SOZ), resected SOZ and all resected channels). Testing was performed by leave-one-patient-out cross-validation and metrics were: (i) area under receiver operating characteristic (AUROC), (ii) area under precision-recall curve (AUPRC) and (iii) Fβ-score.
Results: The ratio of pathologic to normal channels was approximately 1:9 for SOZ, 1:12 for resected SOZ and 1:6 for all resected targets. Considering AUROC, best model performance was achieved for localization of SOZ channels (0.9±0.15 (median±std)), followed by resected SOZ channels (0.88±0.15) and all resected channels (0.84±0.24). Interestingly, model targeting all resected channels achieved the best results for precision-recall metrics (AUPRC = 0.53±0.26, F0.5-score = 0.56±0.23, F1-score = 0.62±0.22 and F2.0-score = 0.72±0.21), despite performing the worst for AUROC. The model localizing resected SOZ channels was ranked second according to AUROC and worst for precision-recall metrics.
Conclusion: We recommend using not only the receiver operating characteristic, but its combination with precision-recall curve and Fβ-score. AUROC informs us on the overall diagnostic ability of the model, AUPRC puts focus on accurate localization of pathologic electrodes and

Fβ-score allows us to specify weights of precision and recall. Sole use of AUROC can be misleading for imbalanced datasets, favoring models with higher ratios of negative cases.

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Number of seizure-free days with adjunctive cenobamate: post-hoc analysis of an open-label extension study

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Purpose: Cenobamate, an antiseizure medication (ASM), is approved in Europe as adjunctive therapy for adults with inadequately controlled focal seizures. Study NCT01866111 (C017) was an international double-blind, placebo-controlled clinical trial with an open-label extension (OLE) that evaluated adjunctive cenobamate in adults with uncontrolled focal seizures. Long-term efficacy of cenobamate was evaluated by percent seizure frequency reduction and responder rates. Reduction in seizure burden measured as the percentage of seizure-free days provides an additional characterization of cenobamate efficacy.
Method: Adults with focal seizures despite treatment with 1-3 concomitant ASMs completed the double-blind treatment period with ≥1 year of follow-up. A post-hoc analysis of seizure-free days in the OLE phase of study C017 compared baseline and postbaseline percentage of seizure-free days.
Results: As of June 2020, 206 participants who entered the C017 OLE had completed ≥4 years of follow-up. Patients taking cenobamate experienced 86.3% seizure-free days compared with 64.4% at baseline. Overall, for participants taking cenobamate throughout the OLE, the odds ratio for having seizure-free days is 3.47 compared to baseline. Results remained consistent throughout the OLE period. The percentage of seizure-free days at year 1 was 83.7% (N=354); year 2, 86.2% (N=272); year 3, 87.3% (N=237); year 4, (87.8% (N=221); and year 5, 88.6% (N=206).
Conclusion: This post-hoc analysis of seizure-free days during the C017 OLE study further supports the efficacy of cenobamate by demonstrating sustained improvement in the percentage of seizure-free days compared to baseline. Treatment with cenobamate can reduce the day-to-day seizure burden in patients with inadequately controlled focal seizures.

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Mes-CoBraD: an open-source research platform for integrated epilepsy-EEG data collection and analysis

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Purpose: Complex brain disorders (CoBraD), as represented in Epilepsy, Neurocognitive and Sleep disorders, have high prevalence, individually and in combination, leading to disability and high socioeconomic burden. The Multidisciplinary Expert System for the Assessment & Management of Complex Brain Disorders (MES-CoBrad) Consortium is an international interdisciplinary project combining Real-World Data from the three conditions. The (MES-CoBraD) platform aims to provide a comprehensive toolset enabling functionalities needed throughout research or diagnostic processes.
Method: A working group on Epilepsy and EEG subject met bimonthly to create a common approach on data collection, visualization and analysis of data from people with epilepsy (PWE) regarding clinical history, seizure semiology and classification, antiseizure drugs and EEG studies.
Results: A template for detailed EEG-Epilepsy data collection from PWE was created providing standardized options through pre-defined lists. Moreover, three self-administered questionnaires were drafted, allowing for screening for possible seizures, phenotyping of seizure events and obtaining detailed clinical and drug history from people with confirmed epilepsy. The 3 questionnaires were implemented in RedCap for administration through tablets. Several open-source and tailormade tools were integrated to address the needs for EEG analysis. Specifically, the tools include EEG signal visualiser and analytics tools, EDFBrowser, python MNE library for artifact repairing, YASA python library for detection of slow waves and spindles and general statistic libraries such as Scipy and Statsmodel for statistical validation.
Conclusion: The MES-CoBraD platform provides tools for harmonized epilepsy data collection and analysis through a single unified environment. Platform's users without significant technical experience or available computational resources will be able to share, review and analyse their data in a unified ecosystem. The platform will be tested and utilized in the process of the MES-CoBraD project in real life use cases validating its usage and functionality.
Acknowledgements
MES-CoBraD is funded with an EU Horizon 2020 grant; ID:965422

Basic Science

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Interictal spikes in animal models of Alzheimer's disease: origin within the dentate gyrus and cholinergic control by medial septum

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Purpose: The origin of interictal spikes (IIS) in animal models of Alzheimer's disease (AD) is not well understood. Here we test the hypothesis that the origin of IIS is along the cortical-CA1-dentate gyrus (DG) dorso-ventral axis. We also tested the novel hypothesis that inhibiting the medial septo-hippocampal cholinergic neurons selectively would reduce IIS because of data showing that the medial septal (MS) cholinergic neurons are overactive when IIS typically occur.
Method: We used Tg2576 mice that simulate a form of familial AD, presenilin 2 knock-out (PS2KO) mice, and the Ts65Dn model of Down's syndrome. For chemogenetic experiments, Tg2576 mice were crossed to ChAT-Cre mice to allow the selective expression of inhibitory Designer Receptors Exclusively Activated by Designer Drugs in MS cholinergic neurons. We recorded EEG along the cortical-CA1-DG axis using silicon probe arrays during wakefulness, slow-wave sleep (SWS), and rapid eye movement (REM) sleep. EEGs were analyzed for the possible occurrence of IIS, and IIS amplitude was quantified along the cortical-CA1-DG axis.
Results: We detected IIS in all transgenic mice but not age-matched controls. IIS were significantly more frequent in Tg2576 mice (vs. PS2KO or Ts65Dn) and REM sleep (vs. SWS or wakefulness). IIS were detectable throughout the cortical-CA1-DG axis although with varying IIS amplitudes. The amplitude of IIS was significantly increased in the DG granule cell layer (GCL) vs. CA1 pyramidal layer or overlying cortex, where IIS amplitude was significantly smaller. Selective chemogenetic silencing of MS cholinergic neurons in ChAT-Cre:Tg2576 transgenic mice significantly reduced IIS frequency during REM sleep without affecting the duration of REM sleep or the number of REM bouts.
Conclusion: Maximal IIS peak amplitude in the DG suggests that the DG could be one of the areas where IIS originate in AD models. Selectively reducing MS cholinergic tone could be a new strategy to reduce IIS in AD.

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A novel method for real-time detection of epileptiform activity in the EEG based on fragmentary decomposition

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Purpose: Timely and accurate detection of EEG events is of special importance in analysis of epileptiform activity. Such tools would help researchers in understanding the mechanisms of epileptogenesis and localization of epileptic zones, and, if performed in real-time in epileptic patients, would allow for prompt alerting and intervention.
Method: We propose a method for real-time detection of specific patterns in the EEG, including various forms of epileptiform activity. The innovative aspect of the method is decomposition of the EEG signal into elementary components (Fragmentary decomposition, FD). FD creates accurate model of the signal and provides more elaborate way for waveform analysis which identifies specific shape of each peak in the time course of nonstationary EEG. The components of the EEG model are then processed by an original temporal pattern recognition algorithm, which may be tuned for recognition of any specific combination of model components. The method and the software may work in real-time (online) and offline processing modes.
Results: The method was successfully applied to automatically find and extract spike complexes in long term recordings from four rodent models of genetic and acquired epilepsies (WAG/Rij, GAERS, Post-SE and PTE) in a study of the frequency properties of the spike-waves. It was revealed that the spike component of the spike-wave has similar frequency properties in all models. In another study the method was used to identify unique patterns at seizure onset in human intracranial and scalp EEG, allowing to detect the seizures at very early stage. In the majority of processed cases (31 patients), the detection occurred a few seconds before the significant increase of spike amplitudes.
Conclusion: This technology may be applied for detection of various events, including interictal or ictal spike-wave complexes, K-complexes, event-related potentials, eye-blinks, etc., and may become a useful tool in many biomedical applications.

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Post-traumatic seizures correlate with underlying neuroinflammation mediated via HMGB1 modulation in a zebrafish model

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Purpose: Traumatic brain injury (TBI) causes lifelong and dynamic effects on one's health and well-being. Neuropsychiatric comorbidities and seizures are common adverse behavioral outcomes post-TBI, yet there is no effective treatment against them. The present study aimed to understand the role of neuroinflammation in TBI-induced spontaneous seizures and associated neuropsychiatric comorbidities.
Method: A weight-drop TBI induction model in zebrafish was used in the study. Moderate group injuries were compared with the sham group. Post-traumatic (PTS) behaviors were

recorded at 0- and 12-days post-injury (dpi). A novel tank test was utilized to measure anxiety, while a mirror bite test was used to measure aggression. Gene expression analysis was performed to assess the role of neuroinflammation in the zebrafish brain samples.
Results: Animals in the TBI group displayed greater recovery time in the recovery tank immediately after the injury. TBI animals also displayed a seizure score of 2 to 5 at 0 dpi, which persisted with a score of 2 to 4 at day 12 dpi. The TBI groups also showed increased turning movement compared to the sham group. The injured animals also exhibited hyperactivity and increased swimming behaviour, indicating seizure and anxiety-like behavioural patterns. The TBI group also spent a long time in the bottom zone of the tank. Besides, the TBI group also showed an increase in the mirror biting frequency indicating aggression-like behaviour. In terms of gene expression, HMGB1, TLR4, and NFKB upregulation were observed in the TBI group as early as on day five post-injury. In contrast, Interleukin-1 was found to be increased on 0 dpi but reduced drastically with time compared to the shams.
Conclusion: Our study depicted post-traumatic seizures with anxiety and aggression, and a correlation of neuroinflammatory mediators, especially HMGB1, was found to have a time-dependent increase. Neuroinflammation may be the key precursor for TBI-associated neuropsychiatric comorbidities.

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Cortical hemodynamic response to seizures is impaired in a rodent model of moderate traumatic brain injury

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Purpose: The hemodynamic response (HDR) to seizures typically includes an increase in cortical blood flow (CBF) to match rising energy demands. However, an impaired HDR to seizures has been reported in the presence of some neuropathological conditions. We hypothesized that prior traumatic brain injury (TBI) increases the likelihood for an abnormal HDR to triggered seizures. Therefore, we investigated the HDR to triggered seizures or cortical spreading depolarizations (CSD), which are common hypermetabolic events associated with brain injury, in a rodent TBI model *in vivo*.
Method: 8–9-week Sprague-Dawley rats underwent a single moderate TBI using a weight drop model (450 g, 102 cm). A separate group of health (sham) rodents received isoflurane anesthesia without closed head impact. Right parietal craniectomy was performed on anaesthetized (1.5% isoflurane in 0.8 L/min O_2) animals to expose the cortex for electrocorticography and laser doppler flowmetry of small pial arteries. 2mM topical 4-aminopyridine application and frontal pole (5 ms pulses, 20 V for 2 s) were used to trigger seizures and CSDs, respectively.
Results: 4-aminopyridine application resulted in seizures in both sham and TBI animals. A significantly higher frequency of seizures was observed in TBI animals (p=0.038). In sham

animals, seizures were associated with a 14.2% (SD=15.9; n=7) increase in CBF over a 1-hour recording period, while in TBI animals the HDR to seizures was inversed, with a decrease of CBF by 2.5% below the baseline (SD=6.3; n=7, p=0.032). CSDs in TBI animals (n=16) were similarly associated with 14% less CBF compared to sham controls (n=16), specifically during the oligemia phase of CSD (p=0.003).
Conclusion: HDR response to seizures and CSDs is impaired in rodents following a single moderate traumatic brain injury. Impaired cerebrovascular response to hypermetabolic events following TBI may increase the risk for progression of brain injury.

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ECoG epileptiform activity in cortical region distal to lesion site predicts epileptogenesis in a translational model of traumatic-brain-injury (TBI)

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Purpose: The latency between TBI and epilepsy onset (PTE) represents an opportunity for counteracting epileptogenesis. However, antiepileptogenesis trials are hampered by lack of sensitive biomarkers to enrich patient's population at-risk for PTE. We studied whether specific ECoG signals predict PTE in a clinically relevant mouse model with ~60% epilepsy incidence.
Method: TBI was provoked in adult CD1 male mice (n=51) by controlled cortical impact (2 mm depth) over the left parieto-temporal cortex, then mice were implanted with cortical screw electrodes (2 perilesional and 2 contralateral to the lesion site). Acute seizures and spikes/sharp waves (SSW) were ECoG-recorded for one-week post-TBI. Data were analysed according to PTE incidence assessed 5 months post-TBI.
Results: Incidence, number and duration of acute seizures were similar in PTE and no-PTE mice, elapsing by 3 days post-injury. Control mice with cortical electrode (naive, n=5) or with electrodes+craniotomy (sham, n=5) exhibited acute seizures but did not develop epilepsy. At perilesional electrodes, the daily number of SSW similarly increased in PTE (n=15) and no-PTE (n=8) mice vs controls ($p<0.05$, n=10) from day 2 post-injury. Differently, at both contralateral electrodes PTE mice showed a progressive increase in the daily number of SSW vs no-PTE and controls. At days 6-7 post-TBI, SSW number was higher in PTE vs no-PTE mice ($p<0.05$) and predicted epilepsy with high accuracy (AUC=0.77, p=0.03; CI 0.5830-0.9670), as also validated in independent TBI-mice (n=23). The daily SSW number at the contralateral electrode showed a circadian distribution in PTE mice increasing during night-time. This circadian pattern was lacking in no-PTE mice.
Conclusion: Data show that epileptiform activity contralateral to the lesion site predicts PTE within 7 days post-TBI. Thus, ECoG monitoring post-TBI in cortical areas outside the primary injury site may provide a biomarker for early identification of individuals at-risk for PTE.

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Dynamics of microRNA expression in patients with epilepsy and focal cortical dysplasia

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Purpose: Focal Cortical Dysplasia (FCD) is brain malformation arising during fetal development, which can lead to seizures and cognitive impairment. Despite previous evidence indicating aberrant miRNA expression in brains of FCD patients, the underlying molecular mechanism and their relationship to seizures remain poorly understood. Through a comparative study across different groups, including FCD1, FCD2, temporal lobe epilepsy- hippocampal sclerosis (TLE HS), and healthy controls, this pilot study aims to get a deeper understanding of the miRNA expression pattern in FCD samples and determine its diagnostic and therapeutic potential.
Method: Brain cortical samples were obtained from FCD patients (n=12; FCD1= 6,FCD2= 6) and healthy postmortem controls (HC) (n=6). To serve as an additional control for comparison, tissues (n=6) from TLE HS patients were collected. Total RNA enriched with small RNAs was extracted from fresh frozen tissues; miRNA sequencing libraries were prepared and subjected to Next Generation Sequencing followed by differential gene expression analyses.
Results: Analysis of miRNA expression profiles was performed on FCD samples, with 11 and 8 miRNAs found to be differentially expressed (DE) in FCD1 and FCD2, respectively, when compared to healthy controls. A significant proportion (75%) of DE miRNAs showed common dysregulation in both FCD1 and FCD2. However, miR-137-3p, -132-5p, and-181a-5p showed distinct dysregulation in FCD1, and miR-451a,-129-1-3p, and-149-5p in FCD2. A comparison with TLE-HS samples revealed that 25 and 31 miRNAs were differentially expressed in FCD1 and FCD2, respectively, with 30% of the DE miRNAs showing distinct expression in FCD1, including miR-106b-5p and -17-5p.
Conclusion: We compared miRNA expression profiles in samples from FCD1 and FCD2 patients to those from healthy and TLE-HS controls. Our results indicate that the distinct differential expression of certain miRNAs in FCD1 and FCD2 samples could serve as potential diagnostic and therapeutic targets for further investigation.

Supported by Ministry of Health of the Czech Republic, grant nr. NU21-04-00305

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Identifying gene regulatory networks impacted across drug-refractory epilepsies

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Purpose: Epilepsy is a chronic and heterogeneous disease characterized by recurrent unprovoked epileptic seizures, commonly resistant to anti-seizure medications. Temporal lobe epilepsy with hippocampal sclerosis (TLE-HS) and mTOR-related malformations of cortical development (termed mTORopathies), including Focal Cortical Dysplasia type IIa and IIb (FCD IIa, IIb) and cortical tubers from Tuberous Sclerosis Complex (TSC), are some of the most common drug-refractory epilepsies. This study is the first to apply a network-based approach across multiple epileptic aetiologies, aiming to improve our understanding of the underlying molecular mechanisms of disease pathobiology, identify impacted biological mechanisms, and apply a causal reasoning framework to identify novel therapeutic targets.
Method: This study collected surgically resected specimens from patients diagnosed with TLE-HS (n = 64), FCD IIa (n = 17), FCD IIb (n = 33), and TSC (n = 21) as well as age-matched autopsy control cortices (n = 14) and hippocampi (n = 13). Gene coexpression modules were used as an unbiased, global model of pathology based on the assumption that biological pathways are dysregulated in the disease state. The systematic comparison of these gene modules enabled the construction of a molecular overview of impaired networks in epilepsy.
Results: The identified regulomes do not only highlight well-described impaired functions in epilepsy, such as neuronal function, energy metabolism and brain extracellular matrix but they also elucidate disease-specific impairments such as the dysregulation of neuronal support and myelination in mTORopathies as well as neuroinflammation in temporal lobe epilepsy with hippocampal sclerosis. These results strengthen the growing understanding of the involvement of the mTORC1 signaling pathway in the myelination process and its deficiency in mTORopathies.
Conclusion: The aforementioned mechanisms are proposed as molecular hallmarks of refractory epilepsies with the identified upstream regulators offering novel opportunities for drug-target discovery and development while supporting the identification of novel treatment avenues.

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Evidence of gut dysbiosis and dysfunction during epileptogenesis in a mouse model

of acquired epilepsy: opportunity for new therapeutic strategies

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Purpose: A dysfunctional gut-brain axis emerges as a novel pathogenic mechanism in epilepsy. In a rat model of status epilepticus (SE) with 60% epilepsy incidence, we found gut structural alterations and inflammation only in animals developing epilepsy, suggesting that gut dysfunctions are specific fingerprints of epileptogenesis. We expanded this evidence in a mouse model of SE with 90% epilepsy incidence, which is suitable for pharmacological studies.
Method: Epilepsy was induced by intra-amygdala kainate provoking SE in C57Bl6 adult male mice. Cortical EEG recording was done (24/7) for 21 days post-SE to allow for spontaneous seizures to develop, then small intestine was analyzed post-mortem in epileptic and saline-injected control mice. Inflammatory markers were measured by immunohistochemistry and RT-qPCR (n=9-10). Quantitative histopathological analysis of gut's structure was performed in hematoxylin-eosin-stained sections (n=9-10). Feces were collected for microbiota analysis using 16S metagenomics, 24 h and 21 days post-SE (n=9-18).
Results: Macrophage Iba1-immunostaining, IL-1β and TNF mRNA were increased in small intestine of epileptic vs sham mice ($p<0.05$) while GFAP+ enteric glia was similar in both groups. Structural changes (reduction in villus height and Goblet cell number, increase in crypt depth) occurred in the gut of epileptic vs control mice ($p<0.05$). Gut microbiota analysis showed reduction of a diversity in epileptic vs control mice ($p<0.01$). At the *Family* level, there was a switch from anti-inflammatory to pro-inflammatory microbiota during transition from SE to epilepsy. Treatment of SE mice with a non-absorbable, gastrointestinal tract-specific antibiotic during epileptogenesis corrected gut alterations and dysbiosis and shortened seizure duration vs vehicle-treated epileptic mice (n=9-10; $p<0.05$).
Conclusion: Epileptic mice showed gut alterations and inflammation during epileptogenesis reflecting a dysfunctional state. A gut-based therapy prevented gut alterations, corrected dysbiosis and reduced seizure duration. Data suggest that gut microbiota represents a therapeutic target in epilepsy.

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The functional role of mutated neurons in the FCD-related ictogenesis

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Purpose: Focal cortical dysplasia (FCD) is one of the leading causes of drug-refractory epilepsy. It is well established that mutations in the mTOR gene represent the molecular substrate

of FCD. The mechanisms of epileptogenicity of the FCD are not well understood. It is hypothesized that neurons carrying the mutation are primarily involved in seizure genesis. In this study, we experimentally tested this hypothesis.
Method: FCD was generated by *in utero* electroporation of mutant mTOR (p. Leu2427Pro) on embryonic day E14.5. Control mice were electroporated with wild type mTOR. Eight weeks postnatally, the mice were implanted with cranial window and epidural electrodes. AAV vector with Channelrhodopsin-2 (ChR2) or hM4Di receptor genes were injected into the FCD lesion. Mice expressing hM4Di receptor received a daily intramuscular injection of deschlorozapine (DCZ, 100 µg/kg) or saline.
Results: The activation of mutated neurons expressing ChR2 using light stimuli (470 nm) was associated with evoked responses in the EEG signal. The application of the train stimuli at frequencies 3, 8, or 20 Hz induced seizures in 80% of FCD mice, with 8 Hz being the most effective frequency. Stimulation with a 590 nm light and stimulation of animals without ChR2, did not generate any evoked response. In control animals, ChR2 activation elicited evoked responses but not seizures. In spontaneously seizing animals, the chemogenetic modulation of mutated neurons resulted in a mild decrease in seizures.
Conclusion: Our optogenetic data suggest that the neuronal population carrying mutated mTOR is functionally interconnected with other neurons in the FCD network and that the mutated neurons play a causal role in seizure genesis in FCD. The mild effect of chemogenetic suppression of mutated neurons on the propensity to seize could be attributed to the limited spatial expression of hM4Di within the FCD.

Supported by grants: (NU21-08-00533, NU21-04-00601), Czech Science Foundation (20-25298S, 21-17564S).

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Interictal EEG features for seizure onset zone localization in neocortical focal epilepsy

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Purpose: For ⅓ epilepsy drug-resistant patients, surgical resection is the primary option to become seizure-free. Seizure onset zone (SOZ) localization is crucial to select the correct target and provide the best possible outcome after resective surgery. Today's clinical convention is

to record and manually review spontaneous seizures recorded by intracranial EEG (iEEG). This approach is time-consuming, depends on experts' experience and is subject to bias.
Method: We retrospectively selected iEEG recordings of 28 neocortical focal epilepsy patients with excellent outcomes (over 1 year seizure free after resection). The model extracts 27 features from interictal segments, each in frequency bands (1-8, 8-12, 12-45 and 55-100 Hz), including approximate entropy, zero-crossing, modulation index, line length, kurtosis, complexity, activity, mobility, skewness, peak to peak, variance, standard deviation, root mean square, the interquartile, minimum, maximum, median, mean, mean dominant frequency in power bands, and each power band's minimum, maximum, standard deviation, median, mean, and interquartile. The Wilcoxon rank sum test was applied to evaluate 8962 channels and the discriminability of SOZ versus nonSOZ for each feature individually. Bonferroni correction was used to avoid multiple comparison problems.
Results: Across all features, the approximate entropy, modulation index, power standard deviation, standard deviation, power maximum, maximum, peak to peak, kurtosis, activity, root mean square, and variance features showed significant differences of mean between SOZ and non-SOZ channels in at least one frequency band.
Conclusion: We examined invasive iEEG recordings of 28 patients with neocortical focal epilepsy and identified features of interictal data that show significant differences between SOZ and nonSOZ channels. These features may prove useful in machine learning approaches to automatically separate electrodes into physiological and pathophysiological signals based on interictal data. These models may be useful for establishing the margins of resection without waiting for seizures and thus reduce recording time, clinician's effort, and patient burden.

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Characterisation of gut microbiome profiles in drug refractory and responsive temporal lobe epilepsy

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Purpose: There is growing evidence suggesting a potential role of the gut microbiome in epilepsy. Potential microbiome-influenced mechanisms in epilepsy include influence of antiseizure medication bioavailability, neuroinflammation, neurotransmitter balance, and hippocampal structural and functional alteration. Here we set out to characterise the gut microbiome profile in patients with epilepsy relative to healthy controls.
Method: Recruiting from outpatient clinics in Beaumont Hospital, Dublin, Ireland, we targeted people with temporal lobe epilepsy (TLE) with MRI findings which are either normal or showed mesial temporal sclerosis (MTS) who were drug-refractory (DR) or drug-responsive (DS). We also recruited healthy controls (HC); participants from the same household of the TLE patients. Faecal samples were collected, and the extracted microbial DNA was sequenced

using Shotgun metagenomic sequencing method. Bioinformatic analyses were conducted to assess the differences in microbial diversity, taxonomic composition, and functional potential.
Results: Sixty-six subjects were included (DR=25, DS=17, HC=24). The number of antiseizure medications were higher in the DR group. There were no significant differences in the antibiotic and dietary intake across the groups. There were no significant differences in the microbial diversity within (alpha diversity) and between (beta diversity) the DR, DS and HC groups. Thirty-one operational taxonomic units (OTU) were differentially abundant when comparing all groups. Eleven OTUs were found to be differentially abundant when comparing patients with and without MTS. Ascorbate and aldarate pathways were relatively depleted in the DS group compared to the DR and HC groups (p=0.03). Glycolysis was relatively enriched in the DS group (p=0.045) and Shikimate pathway showed relative depletion in the HC group (p=0.021). When comparing DR and DS, the biosynthesis of amino acids was enriched in the DR group (p=0.04).
Conclusion: Differences in the gut microbiome composition and function were observed between DR, DS and HC cohorts suggesting the potential role of gut dysbiosis in influencing seizure threshold.

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40 Hz Sensory entrainment impeded kindling epileptogenesis

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Purpose: Patients with Alzheimer's disease (AD) have a higher propensity to develop epilepsy than age-matched controls. 5XFAD mice are an AD model exhibiting rapid amyloid-beta (Aβ) accumulation and a pronounced epilepsy susceptibility. One hour of 40Hz audio-visual stimulation (herein 40Hz) is a novel, non-invasive method to entrain gamma oscillations, increase the microglial phagocytic clearance of Aβ in 5xFAD mice, and modulate glial morphology and expression. We hypothesise that 40Hz will be therapeutic for the epilepsy phenotype of 5XFAD mice via the clearance of pathogenic plaques and, more broadly, by modulating the glial response in epileptogenesis.
Method: 5XFAD mice and wild-type receive 1hr/day 40Hz or darkened chamber (sham) (*n*=7-11/ group), beginning two weeks before and continuing through the electrical amygdala kindling protocol. Kindling consisted of daily electrical stimulation to the amygdala sufficient to generate seizures until the endpoint, five fully generalised class V seizures. Hypointense hippocampal Aβ plaques were imaged with T2* *in vivo* MRI before and after four weeks of 40Hz or sham (*n*=5-6/ group).
Results: 40Hz lowers the class of behavioural seizure at first stimulation (p=0.0425) and increases the number of stimulations required to reach the endpoint (p=0.0164). 5XFAD mice exhibited a higher behavioural class of seizure at first stimulation (p=0.0383), required fewer stimulations needed to reach the first-class V seizure (p=0.0004), and the endpoint (p<0.0001). With *in vivo* MRI analysis, 40Hz reduced average hippocampal plaque size (p=0.0158) and total volume (p=0.0497) compared to sham.

Conclusion: We report a novel finding whereby 40Hz slows the rate of kindling. The 5xFAD genotype expectedly displayed a marked susceptibility to kindling. Since 40Hz slows kindling in both genotypes, our hypothesis that this occurs through glial response modulation is currently under investigation. Further, we have demonstrated a therapeutic effect of 40Hz on hippocampal plaque load, which can be detected with *in vivo* imaging.

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Modelling NMDA receptor activity in focal epilepsy: a resting state study of EEG effective connectivity

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Purpose: The role of N-methyl-D-aspartate (NMDA) receptors in the pathophysiology of epilepsy and seizure generation has been established in pathological and animal models. Recent research has investigated how NMDA receptors modulate brain dynamics in patients with NMDAR autoimmune encephalitis using Dynamic Causal Modelling (DCM) for effective connectivity analysis. With this work, we aim to study regional hippocampal NMDA-dependent effective connectivity in patients with medial temporal lobe epilepsy.
Method: Resting state clinical EEG data and MRI structural brain scans were collected from a cohort of 20 patients with diagnosis of epilepsy and unilateral hippocampal sclerosis. The EEG data were pre-processed to obtain 5-seconds epochs of source-localised electrophysiological activity arising from left and right hippocampus. MRI brain scans were used as the anatomical reference for patient-specific source localisation analysis. We studied individual resting state microcircuitry in the affected (sclerotic) versus non-affected hippocampus using a neural mass model of regional network dynamics. We then performed group-level DCM analysis validating the model with empirical priors.
Results: Our effective connectivity model reproduced patient and area-specific changes in the NMDA-dependent effective connectivity of the hippocampal microcircuitry in patients with focal epilepsy in the absence of evident interictal epileptiform activity. We were able to identify individual differences between the affected and unaffected hippocampi, and to obtain a group effect across the patient population with the use of shared empirical priors. Importantly, these results were found using standard clinical resting state EEG recording.
Conclusion: This work validates DCM as a valuable approach to investigate individual and group resting state EEG network dynamics, in particular in identifying abnormal NMDAR activity using clinical EEG when no obvious interictal epileptiform abnormalities are found.

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CD40 deficiency reduces neuroinflammation in experimental epilepsy

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Purpose: Neuroinflammation is one of the main factors that mediates the development of seizures and epileptogenesis. CD40L-CD40, a familiar member of TNF, increases in chronic epilepsy, after seizures and post-status epilepticus.
The goal of this research was to determine whether the negative modulation of CD40 limits neuroinflammation in a model of epilepsy.
Method: The pentylenetetrazole (PTZ) model of seizure or the pilocarpine model of status epilepticus (SE) were induced in adult male mice deficient of CD40 (CD40KO) and their respective age-gender controls Seizure were analyzed clinically using Racine's score and electrically from local field potential recordings from a silicon probe implanted in the brain. In a group of mice, siRNACD40 or shRNA were injected into the brain before PTZ treatment. Following euthanization, brain samples were processed for histological and biochemical analysis. Secretory sCD40L and a group of cytokines and chemokines were analyzed using ELISA or Meso-Scale Discovery platform. Netrin G2 (NG2) was assessed by immuno-reactivity from brain. ANOVA, Student's t test and Z-scores were used for statistical analysis.
Results: Our preliminary data indicates that CD40 and sCD40L increased after seizures; intracerebral siRNACD40 limits seizure susceptibility and sCD40L concentration in the hippocampus. In addition, CD40KO showed: a) a decreased concentration of pro-inflammatory KC/GRO, IL6 and TNF alpha and increased IL-10 after SE; b) reduction of seizure-induced gamma oscillations in hippocampus and recurrent seizures; c) reduced a chronic brain damage; and d) downregulation of NG2 after seizures.
Conclusion: These data suggest that CD40L-CD40 is an inflammatory hub for the biological mechanism in the development of epilepsy.

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Discovery and characterization of BHV-7000: a novel Kv7.2/7.3 activator for the treatment of epilepsy

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Purpose: Kv7 channels are voltage-gated potassium channels encoded by KCNQ genes that exert physiological control over excitable cells. In the CNS, the Kv7.2 and Kv7.3 subtypes generate M-currents that play a critical role in modulating neuronal hyperexcitability. The Kv7.2/7.3 channel is a clinically validated drug target for treating seizures; however, the need remains for modulators with improved potency, selectivity, and tolerability over activators currently in development.

Method: A screening tier was designed to discover potent and selective Kv7.2/7.3 activators. Fluorescent and electrophysiological assays were employed to characterize lead compounds. Antiseizure efficacy was evaluated in rats in the maximal electroshock seizure model and tolerability was assessed by neurological score (NS). Standard ADME and toxicology assays were used for progressing a drug candidate to the clinic.
Results: Thallium flux screening identified active compounds that were confirmed for activity and further characterized by electrophysiology. BHV-7000 activates the Kv7.2/7.3 channel with an EC_{50} value of 0.6 µM. At 1 µM, BHV-7000 slowed deactivation kinetics from 7.9 ± 1.9 ms to 32.3 ± 6.9 ms and shifted the half-maximal activation potential by -17.8 mV. In rat primary cortical neuron cultures, BHV-7000 produced a concentration dependent hyperpolarization of the RMP. Further, BHV-7000 demonstrated no effect against the human α1β3γ2 GABA receptor and showed no significant activity in off-target panel screens. In the MES model, BHV-7000 provides protection against seizures with a brain EC_{50} of 0.12 µM and a TD_{50} >20 by NS, a sensitive measure of tolerability.
Conclusion: BHV-7000 was rationally designed as a novel activator of heteromeric Kv7.2/7.3 potassium channels and is highly differentiated pharmacologically, biologically, and chemically from other compounds in development. BHV-7000 displays potent antiseizure activity with no overt behavioral effects, favorable ADME parameters, a favorable toxicology profile, and thus represents a promising next generation drug for clinical development.

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Differential microRNA methylation (m^6A) in the brain may contribute to the generation and maintenance of hyperexcitable networks

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Purpose: Epilepsy is one of the most common neurological conditions, affecting ~50 million people worldwide. Evidence is emerging that persistent changes in gene expression regulation and post-transcriptional regulation contributes to the epileptogenic process. MicroRNAs have recently been identified as key regulators of epileptogenesis via altered regulation of gene expression at the post-transcriptional level, however, their regulation during epileptogenesis remains obscure. Preliminary data suggest that microRNAs may be subjected to m^6A (a post-transcriptional modification which regulates RNA fate) and that this process may also be disrupted in epilepsy, representing an unexplored layer of gene expression regulation likely to influence neuronal activity and seizures.
Method: In order to evaluate the effect of m^6A-microRNAs on normal brain behaviour and epileptogenesis, we have profiled hippocampal m^6A-tagged microRNAs during epileptogene-

sis using an adapted m6A-seq approach using the intra-amygdala kainic acid mouse model.
Results: Our analysis revealed extensive differential methylation of microRNAs during epilepsy development suggesting this may be linked to the gene dysregulation which characterises epilepsy. Next, we will determine the physiological relevance of m^6A-microRNAs, their potential role in disease development and whether they may be therapeutically targeted to prevent neurological disease.
Conclusion: This study represents the first microRNA methylation study in the brain, which is hoped will illuminate novel therapeutic strategies for the treatment of epilepsy.

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Neural network architecture optimization with genetic algorithm for improved classification of intracranial EEG events

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Purpose: Recently, neural networks proved to be suitable for an inspection of intracranial EEG (iEEG) interictal periods, a method with valuable diagnostic information for seizure onset zone localization. Here, we propose a genetic algorithm (GA) approach to optimize an architecture of a neural network (P. Nejedly et al. 2019; Scientific Reports 9 (1): 11383) for iEEG processing to improve the classification of different iEEG events.
Method: We use iEEG recordings split into 3-second segments belonging to 4 iEEG event categories. The data includes 94,560 segments of physiological activity, 32,599 artifact segments, 13,489 powerline artifacts, and 52,470 segments with pathological epileptical activity. The data comes from a publicly available dataset recorded at St. Anne's University Hospital, Czech Republic, and includes 30 minutes of relaxed awake recordings from 14 drug-resistant epilepsy patients. The genetic algorithm searches for the best combinations of hyperparameters by evolving through operations such as mutation, crossover, and selection. We optimize hyperparameters of a CNN-GRU model as well as parameters used in short-time Fourier transform and wavelet scattering transform, which we apply to the iEEG signal as part of the preprocessing. The optimized model is then compared to the state-of-the-art CNN-GRU benchmark model.
Results: The GA-optimized model architecture achieved significantly better performance (McNemar's test, $p << 0.001$) with a macro F1 score of (0.9666 ± 0.0012) (mean ± std) compared to the result of the benchmark model (0.9015 ± 0.0027).
Conclusion: We demonstrate the potential of using a genetic algorithm to optimize neural network architecture for iEEG processing as it outperforms the architecture design of a human expert. The GA-optimization provides improvement beyond this classification task, as this model can be further utilized in seizure or noise detectors.

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Fibronectin1-Src kinase axis differentially regulates excitatory synaptic transmission in the hippocampus and ATL in temporal lobe epilepsy

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Purpose: FN1 is an extra-cellular matrix protein that modulates Src kinase via transmembrane integrins. Src family kinases are crucial points of convergence for various signaling pathways. NMDARs, which are regulated by Src kinase, are important in epileptogenesis and play a role in excitatory synaptic transmission in the brain. This study is designed to test the hypothesis that FN1-altered Src kinase functions may contribute to hyperexcitability in MTLE.
Method: Hippocampal and ATL tissue samples from MTLE patients who had undergone surgical resection were acquired for this investigation. Real-time PCR & Western blotting was used to examine the mRNA and protein expression in the hippocampal and ATL areas of both acute and chronic TLE rats and humans. Kinase assay was used to determine functional Src activity. IHC and histopathological examinations were carried out. Functional validation using EPSCs was done using Patch-clamp.
Results: A significant increase in FN1 mRNA was observed in ATL (10.25±1.59-fold, p=0.001) and hippocampus (6.73±2.59-fold, p=0.024) in MTLE patients. FN1 protein levels were significantly higher in ATL (p=<0.01) and hippocampal region (p=<0.01) of MTLE as compared to the control. IHC also revealed upregulation of FN1 protein in MTLE patients. Src was found to be upregulated in the histopathological, immunohistochemical, and protein level findings of the hippocampus. Kinase activity was higher in the TLE model. A significant increase in Src was observed in the chronic model of TLE with no significant changes in the acute TLE model. PP2 blocker resulted in alterations in EPSC from MTS patients.
Conclusion: Our results are indicative of the role of FN1-mediated Src kinase signalling in hyperexcitability via modulating the regulation of NMDA receptors in MTLE. These findings will greatly improve our understanding of the molecular mechanisms and synaptic plasticity involved in the pathogenesis of MTLE, and Src may represent new potential therapeutic drug targets.

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A novel NLRP3 inflammasome inhibitor ameliorates epileptogenesis, depressive-like behaviour and cognitive dysfunction in kainic acid-induced epileptic mice by inhibiting neuroinflammation

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Purpose: The nucleotide-binding domain leucine-rich repeats family protein 3 (NLRP3) inflammasome is an essential target involved in epileptogenesis. Microglia is major source of neuroinflammation following NLRP3 inflammasome activation. Blocking NLRP3 inflammasome activation is considered a viable way to ameliorate epileptogenesis and psychiatric comorbidities. Herein, we intended to explore the neuroprotective role of JC124, a novel NLRP3 inflammasome inhibitor, on epileptogenesis and neurobehavioral comorbidities.
Method: Intrahippocampal kainic acid (KA) injection-induced epileptic mice received JC124 treatment (50 mg/kg, intraperitoneal injection) once daily for 28 days. The spontaneous recurrent seizures of the mice were video monitored. After completion of the treatment, the local field potential of the hippocampus was recorded. Depressive-like behavior was detected with sucrose preference test and forced swim test, cognitive dysfunction was detected with Morris water maze, and anxiety-like behavior was detected with open-field test and elevated plus-maze. Microglia-neuron (BV2-HT22) co-culture system was established to evaluate the anti-inflammatory effect of JC124 in vitro. Cytotoxic effect of JC124 on cell viability was determined by CCK-8 and activation of BV2 cells were induced by Lipopolysaccharides (LPS). The anti-inflammatory and neuroprotective effects of JC124 were detected by western blotting, immunohistochemistry, immunofluorescence, ELISA, cresyl violet staining, FJB staining, TUNEL staining, and electron microscope.
Results: JC124 treatment significantly suppressed epileptogenesis, alleviated depressive-like behaviour and cognitive dysfunction, and decreased hippocampal neuronal loss, microgliosis, and astrogliosis. The protein expression levels of NLRP3, pro-caspasa-1/caspase-1 p20, and gasdermin D (GSDMD)/N-terminal GSDMD, and the pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18 were significantly reduced in the hippocampus of KA-induced epileptic mice after JC124 treatment. Furthermore, JC124 was effective in inhibiting LPS-induced NLRP3 inflammasome activation in BV2 cells, resulting in reduction of neuronal damage and neuroinflammation in HT22 cells.
Conclusion: These data indicated that JC124 inhibited microglia-mediated neuroinflammation. JC124 could be an effective therapeutic agent to suppress epileptogenesis and ameliorate depressive-like behaviour and cognitive impairment.

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c-Abl kinase activation in an epilepsy mouse model is associated with neuronal loss and astrogliosis

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Purpose: Nowadays 30% of epilepsies are refractory, therefore new therapeutic targets and anti-seizure medications (ASM) are needed. Epileptic seizures stimulate an excessive release of glutamate and activate signalling pathways involved in neuron loss and reorganization of excitatory and inhibitory hippocampal circuitry. Recent studies show c-Abl tyrosine kinase activation in epilepsy patients' brain and its involvement in the Pilocarpine induced seizures model. In this work we evaluated the role of c-Abl in the Pilocarpine induced SE model.
Method: To induce status epilepticus (SE) and develop a chronic epilepsy mouse model with spontaneous recurrent seizures, we administered Pilocarpine (350-180mg/kg every 30 min until SE was reached) in 5 weeks old mice. After SE, diazepam was injected i.p (15mg/kg) to halt seizures. Mice's behavior was registered over 15 days and c-Abl activation, neuronal death, inflammation, and glial markers were evaluated in the cortex and hippocampus. We observed c-Abl activation, followed as c-Abl phosphorylated at Tyr412, after Pilocarpine injection.
Results: We found that disrupting c-Abl activity led to fewer seizures, with an increased latency towards SE, and improved animal survival. c-Abl activation correlated with neuronal death, astrogliosis and inflammation assessed by immunofluorescence against NeuN, GFAP and Iba1 in the brain cortex and hippocampus. We also observed that c-Abl inhibition prevented apoptosis, reduced dendritic spine loss, and maintained phosphorylation of NMDA receptor's subunit 2B (NR2B) in *in vitro* models of excitotoxicity.
Conclusion: c-Abl kinase activation in a Pilocarpine-induced chronic epilepsy mouse model is associated with neuronal death and structural alterations in the brain. Overall, our results reveal c-Abl kinase as a regulator of NR2B-NMDAR in excitotoxicity and during SE. These preliminary results present as a new target to develop a novel target ASM.

Acknowledgements: FONDECYT 1201668(AAR), FONDEF ID21I10347(AAR/SZ) and Millennium Science Initiative Program-ICN09_016/ICN 2021_045; FONDECYT 1190334(SZ).

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Upregulation of Calponin-3 aggravates seizure activity

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Purpose: To explore the role of calponin-3 upregulation in susceptibility to epilepsy in C57BL/6 mice.
Method: The expression characteristics of calponin-3 were investigated in a kainic acid (KA) temporal lobe epilepsy model, pentamethazol (PTZ) acute seizure model and PTZ chronic seizure model (kindling model). The adeno-associated virus CNN3 (AAV-CNN3) overexpression vector was used to upregulate hippocampal calponin-3 to observe seizure behavior and electrophysiology in different mouse models.
Results: Compared with control mice, calponin-3 expression was significantly increased in the hippocampus ($p<0.001$) and cortex ($p<0.05$) in the KA-induced model, while there was no significant difference in the hippocampus in the PTZ acute seizures model and PTZ kindling model. Calponin-3 mainly colocalized with astrocytes, but a small amount colocalized with neurons in the hippocampus, and calponin-3 expression was significantly positively related to GFAP expression in the KA-induced model. Compared with AAV-CNN3-con, AAV-CNN3 had a significantly shorter latency period of spontaneous seizures (Racine grade 4 and above) ($p<0.01$), an increased number of spontaneous seizures ($p<0.01$) and an increased number of days with spontaneous seizures ($p<0.001$) in the KA-induced model test. Electrophysiological results showed that the discharge amplitude and frequency of the hippocampus local field potential (LFP) increased in the AAV-CNN3 group, and the frequency of spike emission on the interictal electrocorticogram (ECoG) increased significantly ($p<0.05$). In the PTZ acute seizure model test, the AAV-CNN3 group's latency period was significantly shortened ($p<0.01$), and the spike emission of the ictal ECoG increased. In the PTZ kindling model test, the AAV-CNN3 average Racine grade of seizures was increased at each time point, the latency was significantly shortened ($p<0.01$), and the death rate showed an increasing trend.
Conclusion: Upregulation of calponin-3 in the hippocampus could increase seizure activity and susceptibility to epilepsy.

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Biocompatible probes for neurostimulation: material choice and implantation technique for preclinical application

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Purpose: Temporal lobe epilepsy (TLE) is an adulthood focal epilepsy often refractory to anti-epileptic medications, and mesial TLE (MTLE) is its most severe form, characterized by

hippocampal sclerosis. Neurostimulation technologies are emerging as a critical therapeutic approach for the treatment of drug-resistant epilepsies such as TLE.
Here, we investigated the biocompatibility and techniques for *in vivo* implantation of flexible neuromorphic probes.
Method: *In vitro*, SH-SY5Y cells were plated on glass coverslips treated with three biopolymers (poly (ethyl acrylate) (PEA), polyimide PI-2545 and polyimide HD-4110) and their viability was evaluated.
In vivo, Sprague Dawley rats were implanted with polymer-based probes in basolateral amygdala and ventral CA3. We tested two implantation strategies, one using resorbable stiffeners (silk, alginate, sucrose) and one based on a sewing hole strategy. Immunostaining analyses were performed 2-3 weeks after implantation and cerebral cortex inflammation was evaluated.
Results: Cytotoxicity *in vitro* investigations revealed no significant changes in cells viability in SH-SY5Y cultures plated on PEA and Polyimides.
Probes were successfully implanted *in vivo*, correctly reaching the deep area when the sewing hole strategy was used, while stiffener-coated probes did not match the desired area reliably. Brain tissue implanted with probes, both with or without stiffener coating, showed a minimal biological reaction, such as neuronal cell death and glial cell activation.
Conclusion: PEA and Polyimides are suitable materials for biomedical applications. All probes successfully implanted, with or without stiffener, did not induce any relevant biological reaction. We demonstrated that the “sewing hole” is the ideal strategy to successfully implant flexible probes in precise areas located deep in the brain with minimal invasiveness. Although biocompatible, coating stiffeners do not guarantee sufficient probe rigidity for a reliable insertion into the brain.

The present work was supported by European Union’s Horizon 2020 FETPROACT project HERMES (GA n. 824164).

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Personalized seizure detection using wearable ECG and machine learning methods

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Purpose: Wearable automated detection devices of focal epileptic seizures are needed to alert patients and caregivers and to optimize the medical treatment. Heart rate variability

(HRV)-based seizure detection devices have presented good detection sensitivity. However, false alarm rates (FAR) are too high.
Method: In this phase-2 study we pursued to decrease the FAR, by using patient-adaptive logistic regression machine learning (LRML) to improve the performance of a previously published HRV-based seizure detection algorithm (Jeppesen et al. Epilepsia 2019;60:2105–13). ECG-data were prospectively collected using a dedicated wearable electrocardiogram-device during long-term video-EEG monitoring. Sixty-two patients had 174 seizures during 4,614h recording. The dataset was divided into training-, cross-validation-, and test-sets (chronological) in order to avoid overfitting. Patients with >50 beats/min change in heart rate during first recorded seizure were selected as responders. We compared 18 LRML-settings to find the optimal algorithm.
Results: The patient-adaptive LRML-classifier in combination with using only responders to train the initial decision boundary was superior to both the generic approach and including non-responders to train the LRML-classifier. Using the optimal setting of the LRML in responders in the test dataset yielded a sensitivity of 78.2% and FAR of 0.62/24h. The FAR was reduced by 31% compared to the previous method, upholding similar sensitivity.
Conclusion: The novel, patient-adaptive LRML seizure detection algorithm outperformed both the generic approach and the previously published patient-tailored method. The proposed method can be implemented in a wearable online HRV-based seizure detection system alerting patients and caregivers of seizures and improve seizure-count which may help optimizing the patient treatment.

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Daily intermittent fasting attenuates absence epilepsy in mice

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Purpose: Several studies have shown a tripartite link between food intake, seizures, and cognitive deficits in epilepsy. Absence Epilepsy (AE) affect children during a critical phase of neurodevelopment. Limiting or even avoiding treatments based on antiepileptic drugs with strong side effects is extremely important. We investigated daily intermittent fasting (IF) as an innovative, drug-free method to improve seizure burden as well as cognitive deficits on different mouse models of AE.
Method: We implemented a 1-month daily IF regime (8 h feeding/16 h fasting) in control and epileptic mice followed by a multilevel analysis. We tracked the evolution of seizures (by electroencephalographic recordings) and behavioural comorbidities in the $Grm7^{AAA}$ KI mouse, an isomorphic model of “pure” AE.
Results: We show that the 1-month IF regime significantly reduced the occurrence of absence seizures by ~40%, while improving social and cognitive behavioural scores. RNA-seq experiments and preliminary gene ontology analysis revealed an altered mRNA expression pattern in the thalami of epileptic animals that was reversed by IF. In particular, modifications of angiogenesis-related genes were confirmed by blood vessels tracing experiments. Similar results

were obtained in a pharmacological model of atypical absence seizures, the AY9944 mouse.
Conclusion: Thus, our results indicate that daily IF could be a simple and efficient non-invasive strategy to be proposed as an alternative to the existing, yet often ineffective, anti-epileptic drugs or strict regimes, such as the ketogenic diet.

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RTA 901 as an antioxidant treatment for modifying epilepsy

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Purpose: The generation of reactive oxygen species (ROS) and induction of oxidative stress are common sequelae that occur following brain insult(s) and contribute to the development of epilepsy. Recent studies suggest that NADPH oxidase (NOX) enzyme is a major source of ROS in seizures and epilepsy. Here we study the efficacy of RTA 901, a potential NOX inhibitor, in *in vitro* and *in vivo* seizure models.
Method: *in vitro* experiments were carried out in low-Mg2+ solution to induce seizure-like activity in mixed neuronal cultures prepared from postnatal rat pups. To induce acute seizure *in vivo*, rats were injected with pentylenetetrazol (PTZ). For induction of status epilepticus, kainic acid model was used (KA-SE). Animals were treated with RTA 901 and EEG monitored for up to 15 weeks.
Results: We have shown that preincubation of neuronal cultures with RTA 901 decreased the Ca2+ oscillations, decreased mitochondrial depolarization, and decreased ROS production in a seizure-like activity model. Given 1 hr prior to PTZ-induced seizure, RTA 901 prevented the emergence of seizures in 43% of the injected animals, increased the latency period (the time from PTZ injection until the emergence of seizure), reduced the seizure duration, and attenuated the severity of the seizures. The RTA 901 treated rats displayed a dramatic decrease in seizure frequency after KA-SE in comparison to the vehicle group. 50% of the treated rats were seizure-free 3 weeks after the induction of SE, compared to only 10% of seizure-free rats among the vehicle group. Furthermore, the RTA-treated group displayed a significant increase in the latency period between status epilepticus and the first seizure.
Conclusion: Protective effects of RTA 901 were observed in *in vitro* model of seizure-like activity. Notably, we found that RTA 901 administration modified the development of spontaneous seizures, suggesting the potential for this drug as a disease-modifying treatment in epilepsy.

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Optimisation of Ago-sequencing to define the functional microRNA landscape

during postnatal development

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Purpose: Over the past decade, microRNAs (miRNA) have emerged as important regulators of gene expression in epilepsy. Understanding miRNA-mediated processes in the developing brain may open new possibilities for treatment of early-onset syndromes including genetic epilepsies. This requires an understanding of the miRNA landscape at specific developmental time-points. We previously showed that sequencing of Argonaute (Ago)-bound miRNAs enriches for functionally active miRNAs in adult rodent models. Here, we describe Ago-sequencing optimized for hippocampal miRNA exploration during the first weeks of postnatal development in mice.
Method: Hippocampal tissues were collected from F0.129S6×C57BL/6J mice on postnatal days (P) 0, 7, 15 and 22(n=90) and weighed. Tissues from all age groups were used for the optimization of Ago immunoprecipitation (IP) parameters (antibodies; amounts of protein and beads; centrifugation, etc.) to reduce loss of Ago proteins and increase RNA retention. RNA isolated from immunoprecipitated samples was used for sequencing library preparation using the NextFlex Combo-Seq kit.
Results: Our analyses determined that over 10mg of tissue is required for Ago-IP. While all hippocampi from animals aged P7-P22 surpassed this threshold, 52% of P0 hippocampi weighed ≤10mg. Isolated RNA amount ranged from 1.8–67ng across tested protocols. The immunoprecipitation with anti-pan-Ago (2A8) antibody led to superior purity while shortened centrifugation increased rRNA contamination. Sequencing identified on average 330 miRNA (>10 reads) per sample.
Conclusion: Optimized Ago-Sequencing is suitable for miRNA exploration in the hippocampi of rodent epilepsy models from the day of birth. Utilizing Ago-Seqencing will provide a deeper understanding of miRNA regulation in the developing brain compared with standard miRNA sequencing.

Acknowledgement: This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No [101064343] and was co-funded by Science Foundation Ireland (SFI) under Grant Number 16/RC/3948, the European Regional Development Fund and by FutureNeuro industry partners.

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Neurogenesis in infection-induced epilepsy

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Purpose: The birth of new neurons (neurogenesis) occurs in distinct brain regions such as the subgranular zone of the dentate gyrus throughout adulthood until senescence. Data from experimental models of epilepsy indicate that seizures acutely increase neurogenesis, however cell proliferation may not result in regeneration because cells born during seizures display morphological and functional alterations, which can induce hyperexcitability. There are no data on neurogenesis of infection-induced epilepsy yet, although infections of the CNS are one of the main causes of epilepsy. Controlling neurogenesis after an infection could constitute a promising therapeutic target.
Method: We performed an in-depth characterization of time course and fate of neurogenesis in a model of virus-induced seizures (Theiler's Murine Encephalomyelitis Virus). At 3-, 7-, 14- and 90-days post infection (dpi) C57BL/6 mice were euthanized, and their brains sectioned for immunohistochemical analyses of neurogenesis.
Results: At 3-14 dpi we found cell proliferation within the dentate gyrus to be significantly increased in infected mice. The amount of proliferation was correlated to the temporal proximity of the last seizure. In order to determine the cell fate, we compared the number of newborn neurons, which did not differ significantly between seizing and non-seizing or even mock-infected mice. However, mice with seizures displayed aberrant migration of immature neurons. Moreover, close seizure proximity was also linked to the number of glia progenitors. Seizure severity did not have an impact on proliferation of neurons or glia.
Conclusion: The larger number of cells entering the cell cycle after seizures, as well as their changed migration behavior could contribute to abnormal bursting and self-recurrent seizures. Another mechanism for a pro-epileptogenic influence is differentiation into glia, which contribute to inflammation and disease progression. Further experiments will evaluate whether aberrant neurogenesis can be inhibited, and instead regenerative neurogenesis can be promoted to prevent seizures in infection-induced epilepsy.

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DNA methylation signatures provide new insights into disease mechanisms of MCD and epilepsy

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Purpose: Malformations of cortical development (MCD) comprise a broad spectrum of structural brain lesions and are frequently associated with an early seizure onset. Antiseizure medication is effective in less than 70% of patients and often has adverse effects. No causative or disease-modifying therapy is yet available. DNA methylation signatures in brain tissue obtained from patients with focal epilepsy have been shown specific to and, thus, predictive of the epileptogenic condition and the underlying aetiology. Identifying functional pathways that are targeted by differential DNA methylation will aid in uncovering new insights into

disease mechanisms of distinct MCD histopathological entities and epilepsy and provide the basis for the development of new therapeutic strategies.
Method: We used previously published DNA methylation data (Jabari et al., PMID: 34797422) obtained from a surgical cohort of patients with focal epilepsy and histopathological confirmed MCD, non-MCD with epilepsy (TLE), and non-epilepsy autopsy controls (CTRL). Differentially methylated CpGs sites and regions were selected for functional pathway analysis using GO, Reactome, and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses to infer biological significance and potential mechanisms linking DNA methylation with different brain malformations and seizure phenotype.
Results: Differential DNA methylation in our epilepsy cohort targeted a broad range of biological processes and functional pathways in a pathology-specific manner. More detailed analysis of individual MCD entities disclosed pronounced and remarkable mechanistic differences even between genetically and structurally related lesion types (e.g., FCD 2B and TSC).
Conclusion: Our data suggest that there are pathology-specific molecular disease pathways in MCD. Understanding the molecular basis of different MCD entities will be key for the development of mechanistically informed and thus new personalized therapeutic strategies.

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Comparative analysis of brain and blood-derived DNA methylation signatures in MCD

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Purpose: Epigenetic processes including broad alterations in DNA methylation have been shown to contribute to the pathogenesis of epilepsy; however, considerable gaps remain in our understanding of the precise mechanisms driving this relationship. Furthermore, it remains unknown whether a distinct brain-derived epigenetic profile associated with the epileptic phenotype and underlying etiologies also resides in the blood.
Method: Here, we profiled DNA methylomes in matched brain and blood sample pairs derived from individuals with focal epilepsy and a structural brain lesion (e.g., MCD, glioneuronal tumours, or HS) using Illumina 850K DNA Methylation BeadChip Arrays. We compared these epilepsy-associated DNA methylation patterns in the brain and blood with those of healthy non-epilepsy controls (i.e., autopsy brain samples and a published blood DNA methylation data set) and performed unsupervised UMAP and hierarchical cluster analysis as previously described. Our analysis pipeline was adjusted to control for cellular heterogeneity in both the brain and blood. Other common confounders that we corrected for included sex, age at surgery, and batch.
Results: Our approach identified distinct DNA methylation profiles in surgical brain tissue compared to matched blood samples from the same individuals. Moreover, we provide evidence that blood-derived DNA methylation signatures, despite being very different from the brain, also distinguished epilepsy patients from healthy controls, suggesting that there might

be an intricate molecular connection between the brain and periphery. More samples will need to be analyzed to establish and validate an association with specific lesion types.
Conclusion: This is the first comprehensive analysis of brain and blood DNA methylation profiles in MCD, and other structural brain lesions associated with focal epilepsy and the testing of their diagnostic value. The results suggest great potential towards the future development of DNA methylation-based point-of-care devices and their potential routine application to molecularly support clinical decision-making.

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P2X7 receptor antagonism reduces epileptiform-like activity in human iPSC-derived neuronal in vitro model of epilepsy

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Purpose: **Purpose:** Pharmacoresistance to anti-seizure medications remains a clinical challenge in around 30% of patients. This study aims at identifying whether P2X7 receptor antagonism reduces epileptiform-like activity in hiPSC-derived neuronal in vitro model of epilepsy.
Method: Acute and chronic model of epileptiform activity was induced in hiPSC-derived neuronal networks differentiated for >4 weeks in vitro by treating with 100 µM picrotoxin for 30 minutes or 100 µM picrotoxin and pro-inflammatory agents TNF-α, IL-β and C1q for 10-14 days respectively. The epileptiform-like activity was recorded by patch-clamp technique in the presence or absence of P2X7 receptor antagonist AFC-5128.
Results: In acute model of epileptiform-like activity, application of the P2X7 antagonist AFC-5128 did not show significant differences in the burst frequency (0.03552 ± 0.008 Hz vs 0.04230 ± 0.01 Hz; P =>0.05, n=6), events per burst (10.73 ± 2.225 vs 11.50 ± 1.871; P =>0.05, n=6), burst duration (574.8 ± 160.6 ms vs 571.6 ± 125.9 ms; P = >0.05, n=6) and inter-burst intervals (26501 ± 8279 ms vs 21688 ± 6798 ms; P =>0.05, n=6). In chronic model of epileptiform activity, while AFC-5128 did not show significant differences in the burst frequency (0.07540 ± 0.01680 vs 0.07659 ± 0.02088; P =>0.05, n=9), events per burst (1206 ± 398.0 vs 1061 ± 240.9; P =>0.05, n=9), burst duration (1206 ± 398.0 ms vs 1061 ± 240.9 ms; P =>0.05, n=9) the inter-burst interval showed pronounced difference which is statistically significant (6556 ± 2107 ms vs 39719 ± 15045 ms; P= <0.05, n=9).
Conclusion: This study demonstrates that while antagonism of P2X7 receptors is ineffective in acute model of epileptiform-like activity in hiPSC-derived neuronal network model of epilepsy, it significantly increased the inter-burst interval in chronic model of epilepsy accompanied by inflammation suggesting P2X7 receptors as a potential target for developing anti-epileptic drugs.

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Aminoprocalcitonin protects against hippocampal neuronal death via preserving oxidative phosphorylation in refractory status epilepticus

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Purpose: Refractory status epilepticus (RSE) is a neurological emergency where sustaining seizure causes severe neuronal death. Currently there is no available neuroprotectant effective in RSE. Aminoprocalcitonin (NPCT) is a conserved peptide cleaved from procalcitonin, but its distribution and function in the brain remain enigmatic. Survival of neurons relies on sufficient energy supply. Recently, we found that NPCT was extensively distributed in the brain and had potent modulations on neuronal oxidative phosphorylation (OXPHOS), suggesting that NPCT might be involved in neuronal death by regulating energy status.
Method: In the present study, combining biochemical and histological methods, high-throughput RNA-sequence, Seahorse XFe analyser, an array of mitochondria function assays, and behaviour-electroencephalogram (EEG) monitoring, we investigated the roles and translational values of NPCT in neuronal death after RSE.
Results: We found that NPCT was extensively distributed throughout grey matters in rat brain while RSE triggered NPCT overexpression in hippocampal CA3 pyramidal neurons. High-throughput RNA-sequence demonstrated that the influences of NPCT on primary hippocampal neurons were enriched in OXPHOS. Further function assays verified that NPCT facilitated ATP production, enhanced the activities of mitochondrial respiratory chain complexes I, IV, V, and increased neuronal maximal respiration capacity. NPCT exerted multiple neurotrophic effects including facilitating synaptogenesis, neuritogenesis, spinogenesis, and suppression of caspase 3. A polyclonal NPCT immunoneutralization antibody was developed to antagonize NPCT. In the *in vitro* 0-Mg^{2+} seizure model, immunoneutralization of NPCT caused more neuronal death, while exogenous NPCT supplementation, though did not reverse death outcomes, preserved mitochondrial membrane potential. In rat RSE model, both peripheral and intracerebroventricular immunoneutralization of NPCT exacerbated hippocampal neuronal death and peripheral immunoneutralization increased mortality. Intracerebroventricular immunoneutralization of NPCT further led to more serious hippocampal ATP depletion, and significant EEG power exhaustion.
Conclusion: We conclude that NPCT is a neuropeptide regulating neuronal OXPHOS. During RSE, NPCT was overexpressed to protect hippocampal neuronal survival via facilitating energy supply.

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MicroRNA-mediated inhibition strategies and their neuroprotective potential in epilepsy mouse models

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Purpose: Current epilepsy treatments are mostly symptomatic and do not modify the underlying pathophysiology. Novel approaches modulating multiple targets could provide better therapeutic effects. MicroRNAs (miRNAs) are powerful gene regulators. Previous lab studies have shown that antagomirs-mediated inhibition of miR-324-5p reduces seizure severity in acute and chronic mouse models of epilepsy. Here, we used the same strategy to inhibit miR-324-5p and another microRNA, miR-218-5p to investigate their neuroprotective potential in a genetic-Cntnap2 mouse model. In a different miRNA-inhibition strategy, we used a novel adeno-associated virus (AAV)-microRNA-sponge to investigate cell type-specific (neuron and glial) inhibition of miR-324-5p on seizure susceptibility and neurodegeneration.
Method: For antagomir treatment, Cntnap2 KO and littermate control mice were implanted with EEG electrodes at adult (4-5 months) and older (12-16 months) age points. Post-baseline EEG confirmation, mice were ICV injected with miR-324-5p, miR-218-5p-antagomir and scrambled (SCR) control and investigated for kainic acid (KA) induced seizure susceptibility in younger and seizure numbers in older mice respectively. For AAV-miR-sponge-strategy, 6–8-week-old-C57BL/6 mice were injected with a neuronal (AAV9-Syn-mCherry-miR-324-5p) and glial specific (AAV5-GFAP-mCherry-miR-3245p) sponge and respective SCR-controls via bilateral intrahippocampal injection at the dorsal and ventral hippocampus. Four weeks post-treatment these mice underwent seizure susceptibility using KA and analyzed for cell type-specific expression.
Results: Cntnap2 mice showed an increased seizure onset post miR-218 antagomir treatment compared to SCR control (one-way ANOVA, $p=0.043$) in younger age mice and no difference in the EEG wavefroms was observed (one-way ANOVA, $p>0.05$). Hippocampal cell type-specific-sponge expression was confirmed via mCherry, and a significantly reduced number of seizures ($p<0.05$) was observed in AAV5-GFAP-mCherry-miR-3245p post KA injection, suggesting neuroprotective potential of miR-324-5p inhibition in glial cells.
Conclusion: Our findings illustrate the cell type-specific role of specific miRNAs in regulating seizure susceptibility and severity in mouse models of epilepsy which could help design future therapeutics.

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Central and peripheral circadian clock dysfunction in animal models of genetic generalised epilepsy and temporal lobe epilepsy

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Purpose: Circadian rhythms regulate nearly all biological functions. The core clock gene feedback loop is the molecular basis for circadian rhythms and is present in most cells. The core clock genes include the Circadian-Locomotor-Output-Cycles-Kaput (CLOCK), the Brain and Muscle ARNT-Like 1(Bmal1), Period(Per) and cryptochrome(Cry). Here we investigated clock gene expression in the GAERS model of absence epilepsy and in the kainic acid-induced post-SE model (KASE) of temporal lobe epilepsy (TLE) models of chronic epilepsy models with spontaneous seizures.
Method: Male GAERS and NEC (non-epileptic control), KASE and sham (non-epileptic) were kept in a 7am:7pm light-dark cycle. KASE rats had epilepsy induced at 11-weeks of age. EEG was acquired for 1-week to establish diurnal seizure patterns and to correlate with clock gene expression. At 20 weeks of age, when all GAERS have multiple seizures and all KASE rats develop TLE; hippocampus, hypothalamus, liver, and small intestine were collected. Animals were assigned to different timepoints (n=8 timepoint/strain), and tissue was collected every three hours starting from 7 am throughout the day. qPCR was performed to quantify mRNA expression of the core circadian clock genes Per1, Cry1, CLOCK and Bmal1.
Results: Two-way ANOVA revealed GAERS and NEC strain differences in Per1, Cry1, CLOCK, Bmal1 in all organs($p<0.001$). Per1 was also differentially expressed across the day in the hypothalamus and liver ($p<0.0001$), CLOCK in the hippocampus($p<0.05$) and liver($p<0.001$), and Cry in the hippocampus($p<0.0001$) of GAERS. Cry1 and Bmal1 expression differed in the hypothalamus($p<0.01$) and hippocampus($p<0.0001$) of KASE and sham. Similarly, both genes were differentially expressed across time in KASE rats' hypothalamus($p<0.05$), liver($p<0.0001$) and small intestine($p<0.01$).
Conclusion: We show a significant dysregulation of circadian clock genes in central and peripheral organs of the GAERS and KASE epilepsy models. Further studies should evaluate the effects of those changes on seizure expression and their value as biomarkers of targeted ASM treatment timings.

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Clinicopathological study on microvacuolar changes in the cerebral white matter of patients with epilepsy

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Purpose: Prominent microvacuolar changes in the cerebral white matter are occasionally encountered in the surgical pathology of epilepsy. This preliminary study aimed to investigate the histological details, the prevalence of those lesions, and their possible association with clinical factors.
Method: We retrospectively surveyed surgical specimens of 121 cases in the past three years (2020 – 2022) to identify cases having white matter spongy changes. Histological examination was performed using archival paraffin blocks. Clinical histories were retrieved from patients' medical records, including ages at seizure onset/surgical resection and use of anti-seizure medications.
Results: We found 8 of 121 cases (6.6%) with significant vacuolar changes in the cerebral white matter (mean age at surgery, 19.1 ± 11.6 years; range, 6 – 44 years; mean duration of seizure, 11.9 ± 13.6 years; range, 2 – 43 years). Histological examination revealed myelin sheath ballooning with a well-preserved axon. There were no features of demyelination. There was no significant difference in ages at seizure onset/surgical resection and clinical duration between patients with and without white matter lesions. Almost all patients had been prescribed one or more anti-seizure medications that induce drug-metabolizing enzymes, including carbamazepine, clobazam, and phenytoin.
Conclusion: Low serum folate and high plasma total homocysteine levels have been reported in epilepsy patients taking multiple anti-seizure medications but carrying single nucleotide polymorphism in the gene encoding low enzymatic activity of 5,10-methylenetetrahydrofolate reductase (MTHFR) (Ono H et al. Brain Dev 24, 2002). Histopathological features of microvacuolation in our 8 cases are reminiscence of folate deficiency-associated leukoencephalopathy and may represent an adverse effect of anti-seizure medication. Further study is needed to clarify the relationship between the white matter change and MTHFR polymorphism.

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The antiepileptogenic effects of the gelatinase inhibitor ACT-03 are mediated by reducing gliosis, attenuating inflammation and preserving barrier integrity

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Purpose: Matrix metalloproteinase 9 (MMP-9) play a pivotal role in the development of epilepsy when dysregulated. ACT-03 is a MMP-9 inhibitor with permeability across the BBB (Bertran A et al. BioorgChem 2020; 94:103365). Here, we aim to investigate the ability of ACT-03 to stop or decrease the progression of CNS damage after *status epilepticus* (SE), the epileptogenic process, in preclinical animal models of epilepsy.
Method: We studied the effects of ACT-03 in two preclinical animal models, the intrahippocampal kainic acid (KA) model in mice and the rapid kindling model in rats. The drug was administered once a day for one week or three weeks followed by animal monitoring at different time points for seizure intensity and resistance to kindling, epileptiform activity and behaviour. In addition, we conducted *in vitro* assays in models of BBB breakdown to measure structural and inflammatory markers.
Results: In the rapid kindling experiments, rats treated with ACT-03 showed significantly less intense seizures (Racine scale) than control animals; after a 1-week washout ACT-03-treated animals showed more resistance to kindling than controls ($P<0.05$). In the KA model, animals treated with ACT-03 post SE showed a significant decrease of epileptiform activity which was sustained for several weeks after termination of treatment ($P<0.01$). In accordance, ACT-03-treated animals showed improved cognitive performance compared to control animals ($P<0.05$) (Broekaart DWM et al. J Clin Invest 2021; 131(1)e138332). Histological analyses indicate a trend towards higher neuronal density in ACT-03-treated animals and a significant reduction in gliosis. Mechanistic *in vitro* experiments showed a significant decrease of several inflammation markers (IL-1β, Il-6 and TGFβ-R2) and prevention of BBB leakage under proinflammatory conditions following ACT-03 treatment (Broekaart DWM et al. Biomedicines 2022;10(9):2117).
Conclusion: ACT-03 showed antiepileptogenic effects in rodent models of epilepsy with attenuated seizure-induced cognitive decline, restoration of BBB functioning and without mild or severe side effects.

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Serum cytokines are correlated with epilepsy and rebleeding in cerebral cavernous malformations

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Purpose: Cerebral cavernous malformations (CCMs) may be presented by diverse clinical

manifestations, including epilepsy, intracranial haemorrhage and rebleeding, or asymptomatic. However, it is quite challenging to predict the risk of haemorrhage or seizure for different lesions. Recently, severe studies have suggested that peripheral plasma biomarkers of inflammation may reflect lesion growth, seizure, and recent hemorrhagic activity in CCM patients. The goal of this study is to improve precision treatment of CCM via the identification of biomarkers of the occurrence of intracranial haemorrhage and epilepsy. The purpose of this study is to identify the inflammatory cytokines which are associated with the clinical symptoms, and severity of CCM.
Method: We have recruited 64 CCM patients who has been followed for at least one year and 38 health controls (HC). The serum levels of TGFB1, IFNr, IL-1B, IL-6, TNFa, VEGF, and MMP-1,2,7,9,10 were assessed. The cytokine profiles will be correlated with the occurrence of CCM-related epilepsy (CRE) and rebleeding event (RB).
Results: Comparing with HC, the CCM patients had significantly higher IL-6 (11.4 vs 5 pg/mL, P <0.001), VEGF (64.7 vs 33.2 pg/mL, P <0.01), and TGFB1 (20319 vs 11439 pg/mL, P < 0.001). Among the CCM patients, the serum level of IFNr (CRE 14.9 vs 2.4 pg/mL, RB 16.2 vs 7.8 pg/mL), IL-6 (CRE 16.9 vs 0.9 pg/mL, RB 15.8 vs 9.3 pg/mL), VEGF (CRE 64.4 vs 17.4 pg/mL, RB 97.5 vs 21.6 pg/mL), and IL-1B (CRE 4.8 vs 1.9 pg/mL, RB 5.3 vs 3.0 pg/mL) were substantially higher when the patient had CRE or rebleeding events (P <0.001).
Conclusion: This study revealed that potential of plasma cytokines to be the clinical markers of CCMs, and furthermore to apply cytokine multiplex in the risk assessment and outcome prediction for the patients.

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Microglial-specific knockdown of the core clock gene Bmal1 leads to an increased susceptibility to seizures and behavioural changes in mice

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Purpose: Brain inflammation is an epilepsy hallmark and contributor to the development of seizures. The inflammatory response is primarily mediated by microglia, which are highly regulated by the circadian rhythm, i.e. the 24-hour variations in physiological function orchestrated by a network of autoregulatory genes, including Bmal1. The disruption of circadian rhythms is associated with increased microglial activation and downstream release of pro-inflammatory cytokines. These features contribute to common hallmarks of epilepsy including increased neuronal excitability and disrupted glioneuronal communication. Here we explored the impact of the microglial-specific core clock gene Bmal1 deletion on behaviour and seizure susceptibility in mice.
Method: Twenty male and female young adult (4-month-old) Bmal1-Cx3CR1Cre-ER mice

were bred and daily injected with either tamoxifen (40 mg/kg; IP; 10 days) to induce microglial-specific Bmal1 deletion (Bmal1-KO) or vehicle. Two weeks after recombination, mice underwent behavioural tests to assess, but not only, locomotion and cognition, which were analysed via AnyMaze software. A subset of this cohort was implanted with electrodes for electroencephalographic (EEG) recordings and after recovery underwent the injection of a low dose of kainic acid (KA; IP; 15 mg/kg) to test seizure susceptibility.
Results: Microglial Bmal1-KO mice displayed a hyperactive, but less anxious behavioural phenotype (measured by open field and light-dark box tests) when compared to their littermate controls. This phenotype was driven by females. Bmal1-KOs had an increased susceptibility to develop acute seizures (onset 592.7s ± 139.7s veh; 136.7s ± 27.49s tamox; $P<0.0001$) and a significantly increased seizure severity measured by the total EEG power ($P<0.0002$) after KA administration.
Conclusion: Microglial-specific depletion of Bmal1 led to a disrupted behavioural phenotype and higher propensity to develop seizures in otherwise normal mice. Further studies using continuous video monitoring and long-term EEG will allow to us understand how Bmal1 disruption contributes to the development of epilepsy.

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A comparative study of customized ictal testing battery (CU-ITB) versus conventional ictal testing battery (co-ITB) during ictal phase in localizing seizures in the epilepsy monitoring unit (EMU)

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Purpose: To develop and assess the feasibility of customized ictal testing battery (CU-ITB), to extract maximum information about the symptomatogenic zone during ictal phase of the recorded seizures, in persons with drug resistant epilepsy (DRE).
Method: This pilot non-randomized, cross-over study done in a tertiary care centre, AIIMS, New Delhi, with a comprehensive epilepsy-surgery program. All patients (age > 6 years) with DRE, normal mental status and admitted in the epilepsy monitoring unit (EMU) between January 2018 to July 2019, were requited. Clinical history, home videos, and the questionnaire tool for auras and semiology (QUARAS) were recorded to generate a clinical hypothesis. The EMU staff (non-blinded) applied the CU-ITB in the first, and conventional ITB (co-ITB) for the subsequent ictal event. Seizures were then anonymised, pruned, archived, and stored for analysis by the blinded assessor. Parameters assessed in the CU-ITB were sequenced as per the hypothesized lobe of onset; co-ITB had a random testing sequence. The outcome assessors were blinded to the localization of the symptomatogenic zone, type of battery used, and

received the patient's data sans the seizure numbering or sequence.
Results: Of the 270 subjects screened, 116 (male (69%); mean age: 20.73±8.17years) were recruited. CU-ITB was feasible in 424/498 (85.14%) seizures recorded. A significant association was observed in impaired comprehension (57.8%), ictal palsy (64.4%), impaired registration (55.6%), and impaired orientation (80%) with the frontal lobe, and naming difficulty (51.6%), verbal memory impairment (76.6%) and visual memory impairment (92.2%), with the temporal lobe. In co-ITB, majority (48.3%) of seizures were not localisable except impaired orientation, impaired verbal memory, and impaired repetition with lobe of onset.
Conclusion: CU-ITB was useful in delineating the possible epileptogenic zone and helped gain relevant information from specific lobes within limited timeframe during ictus. Its use was feasible by EMU staff for assessment of most of the seizures.

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Altered spreading of neuronal avalanches in temporal lobe epilepsy relates to cognitive performance: a resting-state hdEEG study

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Purpose: Large aperiodic bursts of activations named neuronal avalanches have been used to characterize whole-brain activity, as their presence typically relates to optimal dynamics and information processing. Cumulative evidence has shown that epilepsy is characterized by alterations of large-scale brain network dynamics, which is related to a reduction of cognitive performance. Here, we exploited neuronal avalanches to characterize differences in the electroencephalography (EEG) basal activity, free from seizures and/or interictal spikes, between patients with temporal lobe epilepsy (TLE) and matched controls. We also related avalanche spreading with the efficiency of memory, often impaired in patients with TLE.
Method: We defined neuronal avalanches as starting when the z-scored source-reconstructed EEG signals crossed a specific threshold in any region and ending when all regions went back to baseline. This technique avoids data manipulation or assumptions of signal stationarity, focusing on the aperiodic, scale-free components of the signals. We computed individual avalanche transition matrices, to track the probability of avalanche spreading across any two regions, compared them between patients and controls, and related them to memory performance in patients.
Results: We observed a robust topography of significant edges clustering in regions functionally and structurally relevant for the TLE, such as the entorhinal cortex, the inferior parietal

and fusiform area, the inferior temporal gyrus, and the anterior cingulate cortex. We detected a significant correlation between the centrality of the entorhinal cortex in the transition matrix and the long-term memory performance (delay recall Rey figure test).
Conclusion: Our results show that the propagation patterns of large-scale neuronal avalanches are altered in TLE during resting state. This suggests a potential application, as for example providing diagnostic hypotheses in those case where scalp electroencephalography monitoring did not result in seizure recording. Furthermore, the relationship between specific patterns of propagation and memory performance supports the neurophysiological relevance of neuronal avalanches.

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Yield of sleep deprivation EEG in suspected epilepsy: a retrospective study

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Purpose: Sleep is an activation procedure and is considered the most potent and best-documented modulator of seizures and interictal epileptiform discharges (IEDs) on electroencephalogram (EEG). The precise role of sleep deprivation in the diagnostic process of epilepsy has not been fully clarified after more than 50 years of use. Sleep deprivation is a procedure that is accompanied by discomfort for patients and their families. Therefore, an accurate indication according to each patient-specific characteristic is needed. This study aims to assess the effectiveness of sleep deprivation EEG in the diagnostic process of patients with suspected epilepsy in our center.
Method: We included patients with a first unprovoked seizure and patients with paroxysmal events suspecting seizures who underwent a sleep deprivation EEG (sdEEG) or routine EEG (rEEG). All patients were subsequently classified with confirmed epilepsy or not.
Results: We included 460 patients. The group with sdEEG consisted of 115 patients, while the group with rEEG comprised 345 patients. In the sdEEG group, 19 patients (17%) were confirmed with epilepsy, of which 17 presented interictal epileptiform discharges (IEDs). For the rEEG group, 66 patients (19%) were confirmed with epilepsy, of which 63 presented IEDs. The difference was not statistically significant.
Conclusion: Our study failed to find a difference in the yield of sleep deprivation versus routine EEG in patients with epilepsy, but there are many significant confounders/sample biases that limit the generalizability of the findings, particularly to the majority of adult practices. Nevertheless, our results also suggest that, at least in younger patients with a first unprovoked generalized seizure, the indication of sleep deprivation should be carefully considered to avoid potentially unnecessary discomfort.

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Delineation of epileptogenic tissue using inter-signal iEEG vector

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Purpose: The patients suffering from focal pharmacoresistant epilepsy are often candidates for epileptic surgery. Precise delineation of the epileptic area remains elusive. In this study we propose a novel bivariate biomarker of epileptogenic tissue derived from a vector which represents delay and information transfer between two iEEG signals.
Method: We analyzed 30-minute resting state stereotactic EEG recordings sampled at 5kHz from 51 patients who underwent monitoring as part of their evaluation for epileptic surgery. The seizure onset zone (SOZ) channels and the resected area under individual contacts was determined by epileptologists. The inter-signal iEEG vector (ISEV), which provides relative amplitude difference and direction metric, was calculated in multiple frequency bands. We assessed the potential of ISEV to delineate epileptogenic tissue - either SOZ or SOZ overlapped with resected tissue in excellent outcome patients (N=19). We compared amplitude and direction values in the whole dataset and individual patients using receiver operating curves and Wilcoxon rank-sum test.
Results: The best ISEV performance was observed in the high gamma band with a significant difference between SOZ and nonSOZ channels (amplitude $p<<0.001$, AUC=0.737; direction $p<<0.001$ AUC=0.595). In the per patient analysis the most patients with significant differences between SOZ and nonSOZ were in the raw signal (30 of 51 patients). The best performance in the subset of patients with excellent outcome was in the Gamma band (amplitude $p<<0.001$, AUC=0.794; direction $p<<0.001$ AUC=0.702) on the group level and in the high gamma band in individual patients (11 of 19).
Conclusion: The proposed novel biomarker could provide a complementary feature for delineation of epileptogenic tissue along with other features. The ISEV does not require complicated detection algorithms verified on gold standard data. The algorithm is therefore clearly defined and extremely fast to compute.

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Suppression of interictal epileptic activity by rapid eye movement sleep shows spatiotemporal divergence

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Purpose: Rapid eye movement (REM) sleep is known to suppress the rate and spatial extent of interictal epileptiform discharges (IEDs). Breakthrough epileptic activity during REM sleep is therefore thought to be most useful for accurately localizing the epileptic focus. Here, we utilized intracranial EEG recordings to investigate the spatiotemporal patterns of IED suppression by REM sleep.
Method: Forty patients with drug-resistant focal epilepsy (19 females; mean age: 36.1±11.1 years) who underwent combined polysomnography and stereo-electroencephalography during presurgical evaluation were included. Ten-minute interictal epochs were selected 2h prior to sleep onset (wakefulness), and from the first and second half of the night during non-REM (NREM) and REM sleep. IEDs were detected automatically on all channels to compare spatiotemporal influences on IEDs.
Results: Overall IED rates and propagation were lowest in REM compared to NREM sleep (p<0.001) and wakefulness (p<0.05). In particular, the suppression of IEDs by REM sleep compared to wakefulness was more pronounced in neocortical (median=-27.6% [range -80.0–383.8]) than mesiotemporal regions (19.1% [-85.7–616.7]) (p=0.01; d=0.39). This was also true inside and outside the epileptic focus (both p<0.05). Across all patients, no novel IED regions were observed in REM sleep versus NREM or wakefulness. Finally, there was a reduction in IEDs in late (NREM: 1.08/min [0.54–3.19]; REM: 0.61/min [0.16–3.03]) compared to early sleep (NREM: 1.22/min [0.44–3.57]; REM: 0.69/min [0.15–3.13]) for both NREM (p<0.001; d=0.24) and REM (p=0.04; d=0.10). This temporal effect was also seen when considering only channels inside or outside the epileptic focus (all p<0.05).
Conclusion: Our results demonstrate a spatiotemporal effect of IED suppression by REM sleep, with a more pronounced suppression of IEDs in neocortical compared to mesiotemporal regions, and in late versus early sleep. This suggests the importance of considering anatomical locations and sleep cycles when using IEDs to define the epileptic focus.

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A machine learning approach in localizing seizure onset zone by cortico-cortical evoked potentials and the brain network alterations in refractory focal epilepsy patients

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Purpose: Accurate localization of the seizure onset zone (SOZ) is a critical factor influencing surgical outcomes of patients with focal refractory epilepsy. In this study, we aimed to develop a new approach for identifying the localization of SOZ based on cortical-cortical evoked potentials (CCEPs) and test its performance in patients with different clinical characteristics.
Method: 50 patients underwent stereo EEG (SEEG) and CCEP procedures were included. Six CCEP measurements were used as input features. This localization model was applied in dif-

ferent clinical phenotypes of focal refractory epilepsy patients. Then, the network patterns derived from CCEPs were accessed on patients with different clinical phenotypes.
Results: The established model accurately localized SOZ in patients with different clinical phenotypes, including pathological types (area under the curve (AUC)=0.93 for focal cortical dysplasia IIa vs. AUC=0.88 for hippocampal sclerosis), surgical outcomes (AUC = 0.92 for seizure-free vs. AUC = 0.92 for non-seizure free), and seizure types (AUC=0.90 for generalized tonic colonic seizure vs. AUC=0.93 for complex partial seizure). The distribution of root means square of the first peak (N1RMS) in the hippocampal sclerosis group was more extensive compared with that of focal cortical dysplasia FCD IIa ($p<0.001$). The sensitivity of localization in the SF group was higher than the NSF group at the individual level ($p=0.036$). Differences in connectivity (measured by N1RMS) between SOZ and nSOZ were more pronounced for complex partial seizure than those for generalized tonic colonic seizure.
Conclusion: This new approach had some improvements in contrast to the limitations of the traditional method of localizing SOZ, including long monitoring time, increased risk of infection due to long-term monitoring, and even the possibility of no spontaneous onset. In addition, our results provide insight into the mechanism of delineating epileptogenicity by CCEPs for patients with different clinical phenotypes.

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Seizure forecasting and detection with wearable devices and subcutaneous EEG – outcomes from the my seizure gauge trial

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Purpose: To develop the ability to forecast seizures in patients with epilepsy without intracranial devices. Seizure forecasting has been established using intracranial EEG, but minimally invasive devices may permit seizure forecasting and provide accurate seizure records.
Method: Patients were recruited for ultra-long monitoring with a wearable device (Empatica E4, Fitbit Charge HR, or Fitbit Inspire) and concurrent ambulatory EEG monitoring (UNEEG SubQ, EpiMinder, NeuroPace RNS) at three sites. Wearable and EEG data from enrolled patients was recorded for 8 months or more. Self-reported electronic seizure diaries and periodic mood and symptom surveys were recorded by participants as well. Recorded data were analyzed to assess the ability to detect seizures, to identify circadian and multi-day cycles, and to forecast and detect seizures.
Results: Thirty-nine patients with epilepsy and one volunteer have recorded over 16000

days (43.8 years) of ambulatory wearable and EEG data, including over 1700 seizures. Nine patients left the study before completion due to device malfunctions, complications, poor adherence, or unanticipated seizure freedom. Analysis in this cohort has established the following:

- Seizure forecasting significantly better than chance in 6 patients with EEG confirmation of seizures using the wrist-worn Empatica E4 device for 6-12 months. Results from a large-scale data science contest on eval.ai will be presented.
- Seizure forecasting using the subscalp EEG significantly greater than chance in 5 of 6 patients with at least four seizures recorded over at least three months using a Bidirectional LSTM neural network.
- Heart rate circadian and multi-day cycles were significantly phase-locked with self-reported seizure likelihood in 10 of 19 patients
- Tonic and phasic electrodermal activity, heart rate, and actigraphy cycles are significantly correlated with iEEG-confirmed seizures in 11 patients measured over at least 8 months.

Conclusion: This project has established the feasibility of forecasting seizures using long-term cycles, wearable devices, and subcutaneous EEG.

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Neurophysiological signatures reflect differences in visual attention during absence seizures

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Purpose: Absence seizures impact 10% to 17% of all cases of childhood epilepsy. Absences affect visual attention and eye movements variably. Here, we explore whether the dissimilarity of these symptoms during seizures is reflected in differences in neurophysiological features and brain network activation.
Method: Pediatric patients with absences performed a 40-minute-long computerized choice reaction time task, with simultaneous recording of 21-channel electroencephalography (EEG) and eye-tracking. We quantified visual attention and eye movements with reaction times and correct responses. Furthermore, we assessed the dominant EEG frequency and the amplitude distribution during seizures. Finally, neural sources and brain networks involved in the generation and propagation of seizures were assessed using dipole fitting, phase connectivity, and graph analysis.

Results: Ten pediatric patients (7-18 years old, 5 females) had absences during the measurement. We observed diverse patterns of eye movements during seizures: five patients had preserved eye movements (preserved group) and five patients showed disrupted eye movements (unpreserved group). In the unpreserved group, EEG amplitude was higher in the posterior channels ($p< 0.05$, mean difference: 193 μV), while the peak frequency was 0.3 Hz lower ($p< 0.05$). Source reconstruction indicated an overall higher involvement of the right frontal eye field for the unpreserved group (1.02% vs 0.34%). Lastly, graph analysis revealed different connections fraction of specific channels, i.e., C4 and Fz for the unpreserved group, and Cz for the preserved group.
Conclusion: We show that the degree of impairment of visual attention and eye movements varies among patients with absences and is associated with differences in EEG features, network activation, and involvement of the frontal eye field. Assessing eye movements and visual attention of patients with absences can be usefully employed in clinical practice for tailored advice to the individual patient.

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Pre-surgical iEEG seizure onset zone localization using deep-learning

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Purpose: Localizing the seizure onset zones (SOZ) is crucial for the surgical treatment of drug-resistant epilepsy. In this study, we introduce an automated method for seizure onset zone localization based on deep-learning evaluation of presurgical iEEG recordings.
Method: We utilized iEEG recordings from 49 patients undergoing presurgical epilepsy evaluation at St. Anne's University Hospital (Brno, Czech Republic). The patients were divided into training (14 patients that were evaluated before 05/2016) and testing set (35 patients that were evaluated after 05/2016) in order to allow for pseudo-prospective testing. We developed a convolutional neural network (CNN) with gated recurrent unit (GRU) to classify iEEG segments as either containing pathological biomarkers (interictal epileptiform discharges and high-frequency oscillations) or not. We then applied this trained model to predict seizure onset iEEG channels in the test set.
Results: We show that the proposed machine learning approach was able to localize SOZ (aggregated good and bad surgery outcomes) with the area under the receiver operating curve (AUROC) 0.87 ± 0.24 (median ± std). The area under the precision-recall curve (AUPRC) is 0.30 ± 0.34, while the AUPRC of the random chance classifier is 0.03 ± 0.03. The results indicate that the proposed method achieved significantly higher AUPRC scores when compared with the random chance classifier (Mann-Whitney U test, $p < 0.001$). Interestingly, we show that the classifier achieved better scores in patients (n=12) with Engel Ia outcome having AUPRC 0.65 ± 0.36, while non-Engel Ia group (n=23) has AUPRC 0.27 ± 0.31.
Conclusion: The proposed approach has the potential to significantly advance the process

of seizure onset zone localization. For example, the method can be utilized for automated processing of long-term recordings, where manual iEEG inspection requires extensive time resources and is subjected to human bias.

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Identification of non-convulsive status epilepticus using functional connectivity

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Purpose: The aim of this study was 1) to investigate the differences in functional connectivity between ictal-interictal continuum (IIC) patients with non-convulsive status epilepsy (NCSE) and those with coma-IIC, and 2) to assess the ability of machine learning based on functional connectivity measures to differentiate between patients with NCSE and those with coma-IIC.
Method: We prospectively enrolled patients with IIC, and we classified the patients with IIC into two groups based on the Salzburg criteria with clinical information: patients with NCSE and those with coma-IIC. We analyzed the functional connectivity based on EEG using graph theory. The EEG signals were converted into images using time-frequency analysis with short-time Fourier transforms for deep learning analysis. We investigated the differences in functional connectivity between patients with NCSE and those with coma-IIC.
Results: We enrolled 72 patients with IIC. Of the 72 patients, 53 patients had NCSE, whereas 19 patients had coma-IIC. Patients with NCSE had decreased global functional connectivity in all frequency bands compared to those in patients with coma-IIC. The machine learning approach based on the functional connectivity measures could classify patients with NCSE and those with coma-IIC with an accuracy of 92.8%, and the accuracy of the CNN models to distinguish them was 73.9%.
Conclusion: We demonstrate that functional connectivity based on EEG using graph theory is significantly different between patients with NCSE and those with coma-IIC. We successfully demonstrate the feasibility of machine learning based on functional connectivity measures to distinguish patients with NCSE and those with coma-IIC.

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Importance of early epileptiform discharges for subsequent non-convulsive seizures: how long to monitor with cEEG?

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Purpose: Non-convulsive seizures (NCSz) is a common finding in patients with otherwise unexplained unconsciousness in the neurocritical care unit. Often continuous EEG (cEEG) is applied for up to 48 h to exclude NCSz, but is this always necessary? We investigated temporal relationship between early epileptiform discharges (EDs) and subsequent seizure-patterns (Szs) in cEEG. We assessed the interobserver agreement for EDs and the change in seizure diagnosis before and after application of the Salzburg criteria. Main question: Is the absence of EDs in the first hour of cEEG recording a reliable predictor of absence of seizure patterns in the subsequent >20 hours?
Method: Retrospective study, cEEGs of more than 20 hours duration obtained in 2013-2015. 101 patients, median age: 64 years (range 1-87 years). Exclusion criteria: postanoxic- or epileptic encephalopathy. Thorough analysis of the first four hours of each recording by two EEG-experts (MF, SB): First ten interictal spikes or other EDs were identified. Whole recording screened for rhythmic patterns fulfilling Salzburg criteria for NCSz. Results then compared to the original (pre- Salzburg) evaluation.
Results: Median duration of cEEG monitoring: 39 h (range 21-374 h). 59 patients eventually had Szs, 90 % of these had their first ED within 10 min, all, but one had either interictal EDs or Szs within 1 h. Median time to first Sz was 10 minutes, 90% started before 110 min. Of 42 patients without Sz, 42% never showed any EDs.
The interobserver agreement on EDs vs no EDs was 87% (Cohen/Conger's Kappa: Substantial: 0.6125). Agreement between original and Salzburg criteria guided diagnosis of seizures was 76% (fair: 0.1621).
Conclusion: Our findings support that 1 h of cEEG is sufficient to decide if further monitoring is required based on occurrence or absence of EDs, since using this approach, we would have missed only one out of 59 patients with Szs.

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Clinically efficient language mapping by electrical cortical stimulation before epilepsy surgery: endorsed by principal component analysis of mapping findings

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Purpose: To clarify anatomo-functional correlation of language areas defined by electrical cortical stimulation (ECS) by means of principle component analysis (PCA) of language tasks.
Method: 12 patients of intractable temporal lobe epilepsy who underwent clinical ECS mapping with subdural electrode placement in the language-dominant hemisphere. 313 elec-

trodes (3-48/patient) were defined as language area by ECS mapping using 6 language tasks. Principal components (PCs) were extracted by PCA and visualized in MNI space. 10 regions of interest (ROI) were delineated, and analysis of variance (ANOVA) on PC scores was performed for 3 language areas (anterior-, posterior-, and basal temporal, language areas (BTLA)).
Results: 3 major PCs were delineated (PC1, 2, and 3 presumably reflecting reading, receptive semantic processing, and expressive semantic processing, respectively).
Anatomically PC1 was prominent at the posterior part of the basal temporal (BT) area and pars opercularis, PC2 at posterior superior temporal gyrus (STG) and anterior BT area, and PC3 at supramarginal gyrus (SMG), posterior middle temporal gyrus (MTG) and whole BT area. ANOVA showed significant interaction between PCs and ROIs. Post hoc analysis revealed functional differentiation in the posterior language area (low PC1 at posterior STG, high PC3 at posterior MTG and SMG) and BTLA (high PC1 and low PC2 at posterior BT area).
Conclusion: PCA revealed 3 independent language functions and indicated functional difference among regions involved in language processing. Clinically, with PCA method, more efficient language mapping which require lesser tasks and provide abundant information is suggested.

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A daily seizure risk forecast from intracranial EEG connectivity during resting-state protocol in focal epilepsy

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Purpose: While traditional seizure prediction methods are usually applied to long-term EEG recordings, here we developed a daily single measure to estimate the risk of upcoming seizure(s).
Our objectives were :
(i) to determine whether patient-specific intracranial EEG (iEEG) connectivity, during daily short periods of vigilance-controlled resting-state, was different between days with and without seizure(s)
(ii) to compare this connectivity-based approach with an interictal epileptiform discharges (IED)-based model
(ii) to prospectively assess its relevance for daily forecasts of seizure risk
Method: Patients and protocol: We recorded daily standardized and controlled 10-min resting-state periods in 10 patients with drug-resistant focal epilepsy who underwent iEEG.
Connectivity and IED features: iEEG connectivity was estimated by means of phase-locking

values between pairs of signals in the standard EEG frequency bands. We also automatically detected IEDs and estimated their number and spread over each recording.
Statistical models: Each 10-min period was labeled as 'preictal' if at least one electroclinical seizure occurred in the next 24h, or 'interictal' if no seizure. The ability of iEEG and IEDs to discriminate between preictal and interictal periods was assessed by a nonlinear support vector machine (SVM) classifier.
Prospective daily forecasts: For each day to predict, we trained SVM models from the previous days and then computed its probability of belonging to the preictal class, reflecting the risk of upcoming seizures.
Results: Connectivity in the theta band was found to provide the best prediction performances (AUC ≥ 0.7 in 80% of patients). In comparison, IED-based models displayed weak performances (AUC < 0.6).
Daily prospective probabilistic forecasts were accurate: mean Brier score and Brier skill score of 0.13 and 0.72, respectively.
Conclusion: Our findings suggest that iEEG connectivity, obtained from vigilance-controlled resting-state recordings, can provide a daily and reliable signature of upcoming seizure(s).

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A machine learning algorithm for detection of ictal and continuum patterns

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Purpose: Machine learning algorithms are transforming the interpretation of EEG and are increasingly valuable for screening high volume critical care monitoring datasets. While classifiers have traditionally focused on classical ictal patterns, it is increasingly understood that periodic and rhythmic patterns also pose clinical risk even when they are inter-ictal and subclinical. Here we describe a classifier model capable of identifying classically ictal, rhythmic, periodic, and sporadic patterns.
Method: We propose a unified classifier model capable of characterizing a continuum of epileptic and nonepileptic abnormalities. Raw EEG time samples from a 10-20 recording configuration are taken as input, and the model outputs the probability that the EEG contains seizure, periodic discharges (PD), rhythmic delta activity (RDA), or any other pattern, for every 1 second in the input recording. In addition, the model outputs whether abnormal patterns are generalized or lateralized. Our outlined model is a 12-layer U-Net with roughly 3.4 million parameters, trained to allow sparse, missing, and multiple expert labels for any given segment. This allows for the utilization of datasets with diverse labelling methodologies. The model was trained, validated, and tested using studies drawn from 6428 subjects (>40,000 labels) selected from our internal Beacon DataStore and the Temple EEG dataset.
Results: Preliminary results demonstrate equivalent to human expert performance in identifying other patterns, and close to human performance for seizure detection. Detection of generalized RDA was superior to PDs and lateralized RDA.
Conclusion: A multiclass classifier capable of identifying ictal and interictal patterns is fea-

sible. We demonstrate a model capable of classifying a continuum of pathological EEG patterns that can be trained on highly diverse labelled data. The incorporation of ictal-interictal continuum patterns is of critical importance given their broad association with neurological risk – making automated identification of these diverse patterns a necessity in critical care medicine.

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Clinical added value of interictal automated electrical source imaging in the pre-surgical evaluation of MRI-negative epileptic patients: a monocentric prospective study

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Purpose: The aim of this prospective study is to assess the clinical added value of a fully automated ESI analysis in the presurgical evaluation of MRI-negative epileptic patients.
Method: All consecutive patients, referred to our Center for pre-surgical evaluation between 15/01/2019 and 31/12/2020, meeting the inclusion criteria, were recruited. Interictal ESI was realized on low-density long-term EEG monitoring (LD-ESI) and, whenever available, high-density EEG (HD-ESI), using a fully automated analysis (Epilog PreOp). The multidisciplinary team was asked to formulate hypotheses about epileptogenic zone (EZ) location at sublobar level and make a decision on further management for each patient at two distinct moments: i) blinded to ESI and ii) after presentation and clinical interpretation of ESI. Results leading to a change in clinical management were considered contributive. Patients were followed up to assess whether these changes lead to concordant results on SEEG or successful epilepsy surgery.
Results: Data from all included 29 patients were analyzed. ESI lead to a change in the management plan in 12/29 patients (41%). In 9/12 (75%), modifications were related to a change in the plan of the invasive recording. Eight out of these 9 patients finally underwent an invasive EEG. In 6/8 (75%), SEEG confirmed the localization of the ESI at a sublobar level. So far, 5/12 patients, for whom management plan was changed after ESI, were operated and have at least one-year postoperative follow-up. In all cases, the EZ identified by ESI was included in the resection zone. Among these patients, 4/5 (80%) are seizure-free (ILAE 1) and one patient experienced a seizure reduction of more than 50% (ILAE 4).
Conclusion: In the presurgical evaluation of MRI-negative cases, interictal automated ESI provides non-redundant information, especially in helping to plan the invasive recording, as long as ESI results are integrated into the whole multimodal evaluation and clinically interpreted.

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Periodic EEG discharges and epileptic spasms involve cortico-striatal-thalamic loops on arterial spin labeling MRI

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Purpose: Epileptic spasms (ES) in clusters and periodic EEG discharges (PD) share many electroclinical characteristics as etiologies, similarity of EEG pattern, periodicity and ictal phenomenology. Their pathophysiological mechanism remains poorly understood. In order to disclose their cerebral generators, we retrospectively analyzed ictal and inter-ictal cerebral blood flow (CBF) changes in pediatric patients having presented generalized or lateralized PDs or ES during arterial spin labelling magnetic resonance imaging (ASL-MRI) acquisition and compared these findings to those of inter-ictal ASL-MRI of patients with drug-resistant focal epilepsy and age-matched healthy controls.
Method: ASL-MRI values were analyzed in cortex, striatum and thalamus, all segmented and divided in six functional subregions: prefrontal, motor (rostral, caudal), parietal, occipital, temporal. Rest CBF values, absolute and relative to whole brain, were compared to those of age-matched controls for each subregion. Ictal exams were acquired in five patients with PDs [subacute sclerosing panencephalitis (1), stroke-like events (3), West syndrome with cortical malformation (1), two of them also had inter-ictal ASL-MRI]; inter-ictal group included patients with drug-resistant ES of various aetiologies (14) and structural drug-resistant focal epilepsy (8).
Results: Main findings were diffuse striatal as well as cortical motor CBF increase during ictal exams in generalized PDs with motor manifestations and focal CBF increase in corresponding cortical-striatal-thalamic subdivisions in lateralized PDs with or without motor manifestations with straight topographical correlation with the EEG focus. For inter-ictal exams, patients with ES disclosed CBF changes in corresponding cortical-striatal-thalamic subdivisions, more frequently when compared drug-resistant focal epilepsies, not related to Vigabatrin treatment.
Conclusion: Our results suggest that corresponding cortical-striatal-thalamic circuits are involved in PDs including ES, opening new insights in their pathophysiology and new therapeutical perspectives. Based on these findings we propose a model for the generation of periodic discharges and of epileptic spasms combining existing pathophysiological models of cortical-striatal-thalamic network dynamics.

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Recurrent isolated sleep paralysis as a clinical expression of focal seizures

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Purpose: According to the International Classification of Sleep Disorders 3, recurrent isolated sleep paralysis (RISP) with or without hallucinations is a REM sleep parasomnia occurring primarily in young subjects with an estimated variable prevalence ranging from 5-40%. It consists of the inability to speak and move upon arousal from sleep, lasting from a few seconds to 2 minutes. However, respiration and consciousness are preserved. Although polysomnography is not mandatory for diagnosis, several symptomatic cases with focal seizures mimicking RISP have already been reported. Hence, we decided to retrospectively review our latest RISP cases considering focal epilepsy in the differential diagnosis.
Method: RISP cases consecutively observed in our Sleep Clinic from 2017-2022 have been reviewed according to their demographic, clinical, and instrumental data, final diagnosis, outcome, and response to therapy.
Results: 10 patients (seven M), mean age 38.4 (16-73), were included with a report of RISP on final or infranight awakenings. The episodes had started at the mean age of 24.1 with variable frequency and duration, respectively, from weekly to monthly and within 30-120 seconds. General comorbid disorders included hypertension, migraine, thyropathy, head trauma, anxiety, and personality disorders, whereas sleep history included arousal parasomnias, bruxism, and OSA. Seven out of 10 underwent brain imaging, and only four displayed microvascular lesions over the frontoparietal region. EEG was negative in six and positive in four with focal interictal paroxysmal discharges.
Three out of 10 also reported waking clinical episodes suggestive of temporal lobe seizures. All but one out of 10 responded positively to therapy, including stress reduction, antidepressants, and antiseizure medications with complete (6) or consistent (3) reduction of RISP.
Conclusion: EEG and neuroradiological screening should be considered in the clinical work-up of patients with RISP, especially when sporadic paroxysmal events have previously occurred during the daytime.

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The role of EEG in the diagnosis of pyridoxine-dependent epilepsy

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Purpose: Pyridoxine-dependent epilepsy with *ALDH7A1* variants (PDE-ALDH7A1) is a rare seizure disorder, typically presenting with severe neonatal seizures. Historically, the response to pyridoxine alone defined the diagnosis, but currently disease-specific biochemical markers and rapid genetic testing are available. Early diagnosis is imperative to prevent uncontrolled seizures and status epilepticus. We have explored the role of EEG in the diagnosis of PDE.
Method: A total of 13 Norwegian patients with PDE-ALDH7A1 were identified, and 94 EEG recordings during the first year of life were reviewed.
Results: The median age at seizure onset was 9 h (IQR 41 h), range 1h-6 days after birth. Median delay from first seizure to first pyridoxine injection trial was two days (range 0-16).
An EEG burst suppression pattern was seen in eight patients during the first 10 days of life.
Eleven had recordings during initial pyridoxin bolus injections:
Immediate EEG improvement was seen in three; two had prompt clinical effect (<1h). In one, no seizures occurred at time of injection.
No change of paroxysmal activity was seen in six; one had prompt clinical effect, one had delayed effect (<1 day), one had no effect, one had uncertain effect, and one had more seizures. One patient had no seizures at time of trial. He remained seizure free for six days.
Two had increased paroxysmal activity, one as a conversion to burst suppression. Both experienced prompt clinical effect.
Conclusion: A burst suppression EEG pattern in neonatal seizures should raise the suspicion of PDE-ALDH7A1. The EEG response during the first pyridoxine trial was variable often with a poor correlation to the clinical effect. EEG non-responsiveness and ambiguous clinical effect should not delay treatment with pyridoxine, which should be continued until results from biomarkers or genetic testing are available.

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Diagnosis of non-convulsive status epilepticus: evaluation of electro-clinical response to intravenous anti-seizure medication in patients with ictal-interictal continuum

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Purpose: The Salzburg diagnostic criteria for non-convulsive status epilepticus (NCSE) were

implemented into the American Clinical Neurophysiology Society Critical Care EEG Terminology 2021. However, the criteria "EEG improvement" and "clinical improvement" in response to intravenously administered anti-seizure medication (IV ASM) in patients with EEG patterns on the ictal-interictal continuum (IIC), representing possible NCSE, have not been operationalized yet.
Method: Participants of the "8th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures" performed a modified Delphi-process to negotiate on a proposal on how to perform the administration of IV ASM for diagnostic purposes and how to interpret results in EEG and clinical response.
Results: Either benzodiazepines or non-benzodiazepine medications can be used as first choice for a DIAGNOSTIC IV ASM trial. Among non-benzodiazepine medications, levetiracetam, valproate, lacosamide, or brivaracetam can be considered. If the first choice fails, another of these IV ASM or a benzodiazepine can be tried.
The dosages and rates of administration of levetiracetam, valproate, lacosamide, brivaracetam, phenobarbital, midazolam, lorazepam, clonazepam, and diazepam are provided. Criteria for EEG and clinical response are defined.
A monitoring time for EEG improvement after a full dose injection is recommended to be 15 minutes for benzodiazepines and of 30 - 60 minutes for non-benzodiazepine medications before switching to the next medication.
Conclusion: The proposed standardized approach of IV ASM administration in suspected patients with IIC aims to prevent over- and underdiagnosis of NCSE. Prospective studies are needed to validate and optimize this approach.

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Recording seizures "in the wild" – electrographic characteristics of ictal subcutaneous EEG recordings

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Purpose: Subcutaneous EEG (sqEEG) is a novel technology enabling prolonged, real-world seizure monitoring. By directly assessing brain activity, sqEEG may have advantages over other mobile technologies, including the potential of characterizing different seizure types and seizure severity. To the best of our knowledge, no previous studies have assessed these capabilities.
Method: Patients with drug-resistant focal epilepsy who underwent ultra long-term sqEEG monitoring in two centres were included. Initial seizure identification was aided by a high-sensitivity detection algorithm. Two raters independently marked each seizure's duration and classified them into three categories: 1 - focal with no/dubious clinical signs, 2 - focal with clinical signs (tonic, clonic or other stereotyped muscle artefact, or arousal) and 3 - focal

to bilateral tonic-clonic. Discrepancies were solved by consensus or by a third reviewer. Patient diaries were examined to assess the proportion of reported seizures.
Results: 322 seizures from fifteen patients were included in the analysis, of which the majority had clinical signs (206 type 2 and 15 type 3). Interrater agreement was high for seizure classification (Cohen's kappa for all seizure types - 0.85; for differentiation between tonic-clonic and other seizure types – 1.0) and for assessment of seizure duration (Pearson's correlation – 0.87). Seizure types and their respective duration were highly individualized between patients. A mixed-effects model with a subject-specific random effect found a significant difference in seizure duration between each of the three seizure types (1<2<3). In this cohort, 25% of seizures were not associated with a diary report in the same calendar day, including 35% of tonic-clonic seizures. A subject-specific random effects model also showed that shorter duration seizures had a lower likelihood of being reported.
Conclusion: These findings suggest that it is possible to categorize seizure types and severity using ultra long-term sqEEG, which may have promising implications for individualized patient management.

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Flash-evoked high-frequency EEG oscillations in photosensitive epilepsies

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Purpose: Epileptic photosensitivity is an abnormal brain reaction to flickering lights, which constitutes the basis of the EEG photoparoxysmal response (PPR) to intermittent light stimulation (ILS). The pathophysiology of photosensitivity is not entirely clear and high frequency oscillations (HFOs), a potential biomarker of the epileptogenic zone, might be useful in unravelling its mechanisms. Aim of the present study is to determine the feasibility of measuring scalp-recorded, flash-evoked, high-frequency EEG oscillations (F-HFOs) using a relatively simple technique. Furthermore, to assess whether F-HFOs are enhanced in photosensitive epileptic patients and if they might be proposed as a putative non-provocative biomarker of photosensitivity.
Method: We studied 34 patients with idiopathic generalized epilepsy (IGE), of which 23 with photosensitivity (IGE+P) and 11 without photosensitivity (IGE-P), compared to 12 patients with temporal lobe epilepsy (TLE) and 22 healthy controls (HS) matched for demographic features. Flash visual evoked potentials (F-VEPs) were recorded from occipital electrodes with eyes closed. We extracted F-HFOs from the broadband scalp of the F-VEP through appropriate filtering. We measured HFO amplitude/number and we carried out a time-frequency domain spectral analysis. Repeated measures ANOVA was applied for statistical analysis.
Results: F-HFOs consistently showed two main spectral peaks (about 85 and 125 Hz) in all groups. The power of the first peak was three times larger ($p \leq 0.002$) in IGE+P compared to IGE-P, TLE patients and HS.
Conclusion: A simplified F-HFO measurement proved feasible in F-VEPs. In IGE+P, enhanced

F-HFOs suggest a role in the generation of the photoparoxysmal response. Some spectral features of the F-HFOs may be proposed as a putative non-provocative biomarker of epileptic photosensitivity.

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Cardiac MRI reveals that heart abnormalities are common in people with epilepsy

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Purpose: People with chronic epilepsy (PwE) have a threefold higher risk of dying from sudden cardiac death (SCD) compared with the general population. Importantly, signs of cardiac damage and electrical instability are increasingly recognized in postmortem analysis and ECG studies of living PwE, which has recently led to the concept of the 'epileptic heart' (Verrier RL et al. Epilepsy Behav 2020;105:106946). Cardiac magnetic resonance imaging (MRI) is an established method for noninvasive myocardial tissue characterization and investigation of myocardial function. The aim of this study was to assess type and frequency of abnormal myocardial structure and function in consecutive living PwE using cardiac MRI.
Method: In this prospective cross-sectional study, 52 PwE aged between 18-60 years without known cardiac disease underwent cardiac MRI at 1.5T. The cardiac MRI protocol included assessment of cardiac function, myocardial edema and fibrosis. In addition, cardiac serum biomarkers were determined and a 12-lead EKG was performed.
Results: Participants (32 female, 20 male) had a mean age of 34.6 years [SD 11.2], mean duration of epilepsy amounted to 16.2 years [SD 11.7]. 11 of 52 PwE (21%) had signs of myocardial fibrosis and 18 PwE (35%) showed signs of diffuse myocardial edema. 11 PwE (21%) had a small pericardial effusion (≤10 mm), and 4 of 52 PwE (8%) showed focal wall motion abnormalities. Cardiac biomarkers and ECGs showed no abnormal findings.
Conclusion: Subclinical myocardial changes are commonly found in PwE. Evidence of myocardial edema and fibrosis might further support the concept of the 'epileptic heart'. Further recruitment of PwE and a detailed risk factor analysis are currently ongoing to identify those PwE who would benefit from cardiological check-ups and therapies, potentially reducing the risk of sudden death in PwE.

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ELEVATE Study 410: Assessment of cognition (EpiTrack®) following perampanel (monotherapy/first adjunctive) in patients with epilepsy and a history of psychiatric/behavioural events

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Purpose: Patients with epilepsy can experience psychiatric/behavioural events and a decline in cognitive function. Here, we present a post hoc analysis of change from baseline cognition (EpiTrack®) scores in a patient subgroup with a history of such events from the Phase IV ELEVATE Study (Study 410; NCT03288129).
Method: ELEVATE was a multicentre, open-label, Phase IV study of perampanel monotherapy or first adjunctive therapy in patients aged ≥4 years with focal-onset seizures (FOS), with/without focal to bilateral tonic-clonic seizures (FBTCS), or generalised tonic-clonic seizures (GTCS), including Titration (≤13 weeks), Maintenance (39 weeks) and Follow-up (4 weeks) Periods. Patients received perampanel at 2 mg/day, up-titrated after >2 weeks to 4 mg/day (further increases of 2 mg/>2 weeks based on response and tolerability; maximum, 12 mg/day). Endpoints included 3, 6, 9 and 12-month retention rate, seizure freedom, median percent reduction in seizure frequency per 28 days, 50% and 75% responder rates, treatment-emergent adverse events (TEAEs), serious TEAEs and discontinuation due to TEAEs.
Results: In the Safety Analysis Set, 54 patients received perampanel monotherapy/first adjunctive therapy. Twenty-four patients (FOS, n=17; FBTCS, n=2; GTCS, n=4) with a history of psychiatric/behavioural events were included in this post hoc analysis. There were no clinically meaningful changes from baseline in EpiTrack® total score at 12 months and end of treatment (mean [SD], -1.1 [3.14] n=11 and 0.5 [2.61] n=23), respectively (increase=improvement). Median percent reduction in seizure frequency/28 days during the entire Maintenance Period was 73.2% (n=22). The incidence of TEAEs in this subgroup was 95.8% (n=23/24), of which the most common were dizziness (25.0%, n=6/24) and vomiting (20.8%, n=5/24).
Conclusion: Perampanel as monotherapy/first adjunctive therapy was generally safe and efficacious in patients from ELEVATE with a history of psychiatric and behavioural events; EpiTrack® scores in these patients were consistent with observations in the overall patient population.

Funding: Eisai Inc.

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Sustained >= 90% response and seizure freedom in patients with focal-onset seizures treated with cenobamate

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Purpose: The maintenance of clinical response over time is a main concern in patients with epilepsy, thus, sustained seizure freedom is the ultimate goal of epilepsy treatment. Unfortunately, many studies failed to show sustained seizure freedom. Here, we analyze sustained seizure control in patients treated with cenobamate.
Method: Adults with focal seizures despite treatment with 1-3 concomitant ASMs completed the double-blind treatment and entered the open label extension (OLE). 354 were included in the C017 OLE modified intent-to-treat population (mITT), 265 originally randomized to CNB, 90 to placebo. All patients underwent a 2-week double-blind conversion to a target dose of cenobamate 300 mg/d. This post-hoc analysis examined sustained seizure response >= 90% and sustained seizure freedom.
Results: During the OLE, >= 90% sustained response for at least one year was achieved by an estimated 38.5% of the patients, and an estimated 23.6% showed sustained seizure freedom. Among these patients, half of them achieved >= 90% sustained response from day 1 and time to achieved sustained seizure freedom,12 months. An estimated 28.4% of the patients achieved >= 90% sustained response for at least 2 years, and 14.3% of being seizure free. Sustained >= 90% response for at least 3-years was achieved by an estimated 23.9% of the patients and 7.5% were seizure-free.
Conclusion: These results suggest that adjunctive cenobamate is a promising drug and may be a suitable long-term treatment for patients with focal-onset seizures to achieve and maintain a high-level of clinical response, including seizure freedom.

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Can antiepileptic drugs improve cognitive functions in elderly with no clinical seizures?

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Purpose: To evaluate whether the introduction of antiepileptic drugs (AED) in small doses can improve cognitive abilities in elderly with mild cognitive impairment and interictal EEG changes but without evidence of clinical seizures.
Method: We performed a six-month prospective study of 48 patients aged ≥60 years (21 women and 27 men, mean age 68.49± 9.27) with the clinical diagnoses of mild cognitive impairment, but not fulfilled criteria for dementia (Mini Mental Score≥24). All patients undergone laboratory data, brain MRI, standard EEG, and WAIS-III subtests for attention, short-term memory and working memory. Majority of patients (39/48, 81,25%) had neurological signs for small vessel disease, and 19 patients (39,6%) had focal or regional interictal activity on standard EEG recording without data regarding clinical seizures. We introduced small doses of AED (up to 100mg of lamotrigine in 12 and up to 200 mg of lacosamide in 7 patients) along with antiplatelet and vasoactive medications. The control group (29 patients with normal EEG finding) was treated with antiplatelet and vasoactive therapy only. Cognitive reassessment was performed after six months of follow up. Two patients stop taking AE drug during the

follow up period due to side effects.
Results: Favorable cognitive outcome had 11/19 (57.89%) in AED group, comparing to 6/29 (20.68%) in control group (p=0.019). Improvement was noticed in domains of attention and working memory, but not in verbal memory (p=0.1599). Logistic regression model showed that factors affected the outcome were presence of interictal EEG findings and usage of AED (p<0.001) but we did not find the difference regarding the gender, age, or presence of neurological signs for small vessel disease.
Conclusion: We found that introduction of small doses of AED in patients with mild cognitive impairment who had interictal EEG changes without clinical seizures, could improve cognitive functions in domains of attention and working memory.

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Rescue medication for seizure emergency management in the UK community: a CPRD retrospective database study

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Purpose: Assess prevalence, demographic/clinical characteristics, and health care resource utilization (HCRU) of patients prescribed rescue medications (RM) for emergency seizure-management in UK.
Method: Retrospective cohort study using general practice data from Clinical Practice Research Datalink (CPRD-Aurum) and Hospital Episode Statistics (HES). Patients with ≥1 recorded RM-prescription (buccal midazolam [bMDZ]/rectal diazepam [rDZP]/off-label oral benzodiazepines [oBZD; diazepam/lorazepam/clobazam/clonazepam]) between 2016-2020 were included. Patients were followed from index (date of first RM-prescription) to death, date of last available practice data in CPRD-Aurum, end of study period, or one year from date of last RM-prescription.
Prevalence of RM-prescription (number of patients with epilepsy and RM-prescription/total number of patients with epilepsy) was calculated using CPRD-Aurum data for 2019. HCRU analysis (inpatient/outpatient/A&E) used cohort data linked to HES.
Results: In 2019, prevalence of RM-prescription among patients with epilepsy in UK community was 6.7% (9336/139,667). bMDZ was most prevalent RM (4.8%).
Between 2016-2020, 26,534 patients with RM-prescription were identified in CPRD-Aurum (mean age: 41.5 years; 50.3% male); 43.0% were new RM-users (no recorded RM-prescription one-year pre-index). Mean age of patients with bMDZ/rDZP/oBZD-prescription (n=16,092/5044/5398) was 32.0/61.5/51.0 years. bMDZ was prescribed to children and adults (44.2%/55.8%). rDZP and oBZD were mainly prescribed to adults (93.3%/99.5%). Diazepam was the most prescribed oBZD used as RM for emergency seizure-management (97.5%, 5264/5398). Among patients with RM-prescription (n=26,534), 35.5% had no anti-seizure medications at index (monotherapy/polytherapy: 22.3%/42.1%).
Among patients with RM-prescription and HES linkage in 2019 (n=11,594), 25.1% had

≥1 epilepsy-specific inpatient hospitalization (mean[SD]/median[IQR] hospitalization days=14.8[34.2]/2.9[12.0]); 35.7% had ≥1 neurology-specific outpatient visit (mean[SD]/median[IQR] visits=4.0[4.5]/2.6[3.4]); 8.7% had epilepsy-related emergency attendance (mean[SD]/median[IQR] attendances=4.9[5.4]/3.0[4.0]); and 7.8% had A&E arrival by ambulance due to epilepsy (mean[SD]/median[IQR] arrivals=3.8[4.4]/2.2[3.4]).
Conclusion: Prevalence of RM-prescription among patients with epilepsy in UK community was 6.7%. Despite RM availability, patients encounter challenges to manage seizure emergencies (shown by HCRU) highlighting need for faster emergency medications.

Funding: UCB Pharma-sponsored.

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A case-control study developing a clinical prediction model for epilepsy-related deaths: the Scottish epilepsy deaths study (SEDS) score

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Purpose: This study develops a clinical prediction model (CPM) to identify adults at increased risk of epilepsy-related death within the next seven years, thereby aiding clinicians (including non-specialists) in prioritising their care.
Method: In this age-/sex-matched case-control study, we compared adults (aged ≥16 years) suffering epilepsy-related death between 2009-2016 to living adults with epilepsy in Scotland. Cases were identified from administrative national datasets linked to mortality records. ICD-10 cause-of-death coding was used to define epilepsy-related death. Controls were recruited from a research database and epilepsy clinics. Medical records were abstracted. Univariable and multivariable conditional logistic regression were undertaken to develop a CPM consisting of four variables chosen *a priori* (SEDS score), using a weighted sum of the factors present. Odds ratios (OR) were estimated (95% CIs).
Results: 224 deceased cases and 224 controls were compared (mean age 48 years, 114 male). In univariable analysis, predictors of epilepsy-related death included recent epilepsy-related hospital attendance (OR 5.1, CI 3.2-8.3), high deprivation (OR 2.5, CI 1.6-4.0), developmental epilepsy (OR 3.1, CI 1.7-5.7), raised Charlson Comorbidity Index (CCI) score (OR 2.5, CI 1.2-5.2), alcohol abuse (OR 4.4, CI 2.2-9.2), and absent recent neurology review (OR 3.8, CI 2.4-6.1). SEDS Score model variables were derived from the first four listed above, with CCI ≥2 given 1 point, high deprivation 2 points, developmental epilepsy 2 points, and recent epilepsy-related hospital attendance 3 points. Compared to a SEDS Score of 0, those with a SEDS

Score of 1 remained low risk (OR 1.6, CI 0.5-4.8). Those with a SEDS Score of 2-3 had moderate risk (OR 2.8, CI 1.3-6.2). Those with a SEDS Score of 4-5 and 6-8 were high risk (OR 14.4 (CI 5.9-35.2) and 24.0 (CI 8.1-71.2), respectively).
Conclusion: SEDS Score may be a pragmatic tool for identifying adults at high risk of epilepsy-related death and requires external validation.

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Cultural aspects of epilepsy management among school children in Egyptian rural communities: a cross-sectional community-based study

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Purpose: Despite the recent advances in the medical treatment of epilepsy which enable most patients to lead reasonably typical family and working lives, the illness is still regarded by many mysterious, frightening, and even shameful conditions. This study aimed to investigate the prevalence of epilepsy among Egyptian schoolchildren and the common beliefs and traditions that were associated with it.
Method: This study was conducted as a cross-sectional study to assess the families' beliefs, attitudes, and practices of epileptic children. A self-administrated questionnaire was used for that purpose. Risk factors for epilepsy and the factors that affected the outcome of epilepsy were studied and analyzed.
Results: Among the screened 30410 students, 170 students, with a mean age of 10.2 ± 1.9 years, were confirmed to have epilepsy with a prevalence rate of 0.559%. The most commonly known etiology was hereditary (14.8%) followed by head trauma (10.1%), while brain tumor and arteriovenous malformation were reported in 4.1% and 3.5%, respectively. The epilepsy was associated with ictal injuries (37.03), urine incontinence (29-62%) and tongue biting (22.35%) and postictal sleepiness (32.91%), headaches (22.94%), and Todd's paralysis (4.11%). Interestingly, 74.7% of epileptic students did not receive any medical treatment, while 18.8% did not receive appropriate treatment. The families of 77.16% of these children did not know about the diagnosis. The family of 113 children frequented charlatans thinking that epilepsy was an incantation. Financial problems were the cause of non-adherence to the treatment in 13.5% of the children
Conclusion: Epilepsy is not uncommon among schoolchildren in rural areas. There are many cultural, social, and economic problems as regards epilepsy and its management in rural communities that urge the need for health education and proper management.

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What should preconception healthcare for women with epilepsy consist of? A multi-stakeholder consensus view from the UK

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Purpose: To gain consensus on the content of preconception care, when to intervene and to understand the outcomes of importance for women with epilepsy in the UK, aiming to reduce missed opportunities and variation of care to improve maternal and child outcomes before conception.
Method: Stage 1 involved thematic analysis of data gathered from 35 interviews and three focus groups with women with epilepsy, their partners and family, and data extracted from 22 full-text papers included in a mixed-methods literature review comprising 2,008 women with epilepsy. These datasets generated a long list of intervention items, coded into domains using COMET taxonomy to develop and pilot the survey. Stage 2 involved a two-round online Delphi survey with healthcare professionals, voluntary organisations, and women with epilepsy and their significant others to prioritise the content of preconception care. Stage 3 involved an independently chaired Consensus meeting with stakeholder representatives. The James Lind Alliance's methodology informed its format.
Results: Two hundred forty-eight key stakeholders completed two survey rounds, rating 47 items relating to the content of preconception care on a 9-point Likert scale. Thirty-one items of preconception care were rated "essential" by >80% of survey participants, and a further five items were voted essential at the consensus meeting. The essential domains include:
· "Access and Availability of Preconception Care" (4 items)
· "Contraception Review" (5 items)
· "Information Needs" - relating to epilepsy and medicines in pregnancy (6 items)
· "Managing-pregnancy-and-seizure-related-risk" (3 items)
· "Optimising seizure control" (11 items)
· "Preconception care pathway" relating to individualised, flexible care responsive to changing circumstances (4 items)
· "Support for planning" - exploring concerns relating to pregnancy with epilepsy (4 items).
Conclusion: Consensus on the content of preconception care was achieved, warranting further research and feasibility testing of targeted preconception health messages to increase pregnancy planning for women with epilepsy and health professionals involved in their care.

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Antiseizure medication regimen in planned vs unplanned pregnancies in women with epilepsy

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Purpose: To assess if antiseizure medication (ASM) regimens in pregnant women with epilepsy (PWWE) are associated with planned versus unplanned pregnancies. We hypothesized that planned pregnancies would be associated with ASM regimens with the most favorable safety data for child outcomes.
Method: The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study is a prospective, observational, U.S.-based multi-center investigation of PWWE and their children. For this secondary analysis, we categorized ASM use at conception into two groups based on safety data. Group 1: lamotrigine and/or levetiracetam, or no ASMs; Group 2: other ASMs. A logistic regression model predicting odds of planned pregnancy was conducted, unadjusted and adjusted for covariates associated with planned pregnancies.
Results: 334 PWWE were analyzed. 170/239 (71.7%) pregnancies were planned in Group 1 versus 58/95 (61.6%) in Group 2. The unadjusted odds ratio (OR) of planned pregnancy for Group 1 versus Group 2 was 1.57 (95% CI 0.95-2.59, p-value=0.075). Covariates associated with planned pregnancy include married/cohabiting relationship (OR 3.96, 95% CI 1.98-7.90, p-value<0.001), college degree (OR 2.89, 95% CI 1.39-6.04, p-value=0.005), advanced degree (OR 5.82, 95% CI 2.17-15.59, p-value<0.001), and black race (OR 0.27, 95% CI 0.10-0.74, p-value=0.012). Covariates were similar between groups, although Group 2 showed a trend toward higher proportions with no college degree (37.9% versus 27.2%) or not married/cohabiting (25.3% versus 20.5%). After adjustment for covariates, the OR of planned pregnancy for Group 1 versus Group 2 attenuated to 1.35 (95% CI 0.75-2.44, p-value=0.316).
Conclusion: The odds of a planned pregnancy was not significantly different between PWWE on an ASM regimen with favorable safety data versus other ASM regimens in MONEAD. However, the proportions of planned pregnancy for both groups and proportions of PWWE on favorable ASM regimens were relatively high. This hypothesis should be re-evaluated in other, less-selective PWWE populations and in different geographic regions.

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Changes in total daily dose of lamotrigine and levetiracetam during pregnancy: reflection on current clinical practice at US tertiary epilepsy centers

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Purpose: To characterize changes in total daily doses of lamotrigine(LTG) and levetiracetam(LEV) during pregnancy in individuals with epilepsy.
Method: Individuals receiving LTG or LEV during pregnancy as monotherapy or polytherapy enrolled in the 20-site prospective, observational Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study were included in the analysis. The primary outcome of interest, total daily dose; was compared between trimester 1,2, and 3 visits using linear mixed effects modelling with trimester as a categorical variable and subject-specific and site-specific random intercepts. Tukey post hoc test with a two-sided significance level P <0.05 was used for multiple pairwise comparisons amongst trimesters.
Results: 172 LTG and 154 LEV patients met criteria and were included in the analysis. The mean (standard deviation: SD) total daily LTG dose during trimesters 1, 2 and 3 were 421mg (196), 547mg (277) and 657mg (332) respectively. LEV mean (SD) total daily doses were 2105 mg (1062), 2119mg (1158), and 2478mg (1253) during trimesters 1, 2 and 3 respectively. Multiple comparisons across all trimesters showed a significant difference (p<0.001) in total daily doses between every trimester for LTG and trimesters 1 and 3 (p<0.001) and trimesters 2 and 3 (p<0.001) for LEV.
Conclusion: There were larger adjustments in total daily dose during pregnancy in patients receiving LTG (56% increase) than LEV (17% increase). Changes in dosing were determined by the treating physician in tertiary epilepsy centers in the United States, thus are indicative of clinical practice

Funding: Supported by grants (U01-NS038455 and U01-NS050659) from the National Institutes of Health: National Institute of Neurological Diseases & Stroke, and National Institute of Child Health & Development; National Institute of Child Health & Development R01HD105305; ClinicalTrials.gov, NCT0730170.

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Association of prenatal valproate exposure with risk of epilepsy in children of affected mothers

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Purpose: Use of valproate in pregnancy is associated with increased risks of abnormal fetal brain development with potential long-term implications for the child. We aimed to examine whether use of valproate in pregnant women with epilepsy contributes to epilepsy risk in their children.

Method: We carried out a prospective population-based register study within the SCAN-AED project, of children born in Denmark, Finland, Iceland, Norway and Sweden between 1996 and 2017. Maternal use of valproate and other antiseizure medication (ASM) was defined as any redeemed prescription from 30 days before pregnancy to birth and the mean daily dose was defined as the sum of doses from all prescriptions during this period, divided by the number of days. Assessment of epilepsy in children and their mothers was based on ICD-10 diagnoses (G40-G41) from specialized care and ASM reimbursed for epilepsy. Adjusted hazard ratios (aHR) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models.

Results: Among 4,491,770 live-born singletons, we identified 38,660 (0.9%) children of mothers with epilepsy, of whom 1,950 were prenatally exposed to valproate. Among children of mothers with epilepsy, there was an increased risk of epilepsy in children prenatally exposed to valproate versus children with no prenatal ASM exposure (aHR=2.15, 95% CI: 1.66-2.78) and versus children with prenatal lamotrigine exposure (aHR=1.52, 95% CI: 1.08-2.14). Epilepsy risk did not increase with the estimated mean daily dose of valproate (reference: no prenatal ASM exposure versus <750 mg: aHR=2.11, 95% CI: 1.49-2.98; 750 to <1500 mg: aHR=2.19, 95% CI: 1.55-3.07; ≥1500 mg: 2.18, 95% CI: 1.31-3.62).

Conclusion: Prenatal exposure to valproate was associated with an increased epilepsy risk in children, but not in a dose-dependent manner. To disentangle the potential contribution of valproate to offspring epilepsy risk from genetic risk of epilepsy, we will apply sibling comparisons and negative controls in further analyses.

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Maternal folic acid supplementation and risk of attention-deficit/hyperactivity disorder (ADHD) in children prenatally exposed to antiseizure medication. A population-based cohort study of more than 3 million children

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Purpose: The objective was to investigate whether high-dose periconceptional folic acid use is associated with reduced risk of ADHD among children prenatally exposed to antiseizure medication (ASM).
Method: We carried out a population-based cohort study including children born in Denmark, Iceland, Norway, and Sweden between 1997 and 2017, using register data in the SCAN-AED project (www.scanaed.org). We defined prenatal exposure to ASM as any filled prescription for ASM from last menstrual period (LMP) to birth, and use of periconceptional high-dose folic acid as any filled prescription for folic acid ≥1 mg, between LMP-90 days and LMP+60 days. Diagnosis of ADHD was based on ICD-10 codes from the specialist care. Cox proportional hazard regression provided adjusted hazard ratios (aHR) and 95% confidence intervals (CIs).
Results: From a cohort of 3,317,725 children, 15,627 children were prenatally exposed to ASM. Among ASM exposed children, the aHR for ADHD was 0.80 (95% CI 0.63-1.02) for children exposed to high-dose folic acid (n=4,701, incidence rate per 1000 person years [IR]: 3.33 [95% CI 2.75- 4.02]), compared to children unexposed to high-dose folic acid (IR 4.65 [4.19-5.17]). For lamotrigine monotherapy (n=6,375), the aHR for ADHD was 0.48 (0.27-0.87) (IR 1.62 [1.01-2.61]) in children exposed to high-dose folic acid versus IR 4.03 (3.33-4.88) in children unexposed to high-dose folic acid. For carbamazepine monotherapy (n=1,499), the aHR was 0.99 (0.52-1.89) (IR 3.66 [2.44-5.51]) in children exposed to high-dose folic acid versus IR 4.43 (3.11-6.29) in children unexposed to high-dose folic acid. For valproate monotherapy (n=960), the aHR was 0.84 (0.39-1.83) (IR 3.74 [2.26-6.21]) in children exposed to high-dose folic acid versus IR 5.77 (4.06-8.21) in children unexposed to high-dose folic acid.
Conclusion: Periconceptional high-dose folic acid was associated with reduced risk of ADHD in children prenatally exposed to lamotrigine, but not in children exposed to carbamazepine or valproate.

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Neurodevelopmental outcomes in children and adults with fetal valproate spectrum disorder

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Purpose: Prenatal exposure to valproate is associated with a higher risk of altered neurodevelopmental outcomes including in cognitive, motor and social development. However, there is limited information on the neurodevelopmental profile of children and young adults exposed to valproate in utero and who were diagnosed clinically with Fetal Valproate Spectrum Disorder (FVSD, ICD 11 LD2F.03).
Method: This was a cross-sectional, observational study investigating neurodevelopmental outcomes in children and adults with a diagnosis of FVSD. It was co designed with mothers of children with FVSD. A web-based questionnaire was built including the Patient Reported Outcomes Measurement – Perceived Cognitive Function (PROMIS-PCF), the MacArthur Health Behaviour Questionnaire and the Pediatric Symptoms Checklist, along with questions regarding physical health and sensory functioning.
Results: 90 parents or caregivers completed questionnaires regarding 146 children and young adults (mean 18.1 years, range = 7-37 years). Within the group with an FVSD diagnosis (n=99), 75.8% were exposed to valproate monotherapy and the mean daily dose of valproate was 1474 mg/d.
The mean score on the PROMIS-PCF was 38.5 (SD = 8.8) for those with FVSD, with 43.3% scoring in the moderate impairment range and 14.4% within the severe range. Rates of autistic spectrum disorder and attention deficit hyperactivity disorder were high at 62.9% and 24.5% respectively. Sensory difficulties were high (80.6%) and individuals with FVSD required a range of health services, the most frequent being speech and language therapy (87.8%). Twelve individuals with FVSD had developed epilepsy themselves.
Conclusion: Neurodevelopmental difficulties and disorders are a central and significant feature of FVSD. Children and young people with FVSD require diagnosis and clinical management within specialist multidisciplinary teams due to the board range of physical, cognitive and social features within FVSD.

Epilepsy in Older People

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Impact of seizure recurrence on 1-year functional outcome and mortality in patients with poststroke epilepsy

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Purpose: To prospectively investigate the functional outcome and mortality of patients with poststroke epilepsy (PSE) and analyze the effect of seizure recurrence on the outcomes.
Method: This is part of the Prognosis of Post-Stroke Epilepsy study, a multicenter, prospective observational cohort study, which involved 392 patients with PSE (at least 1 unprovoked seizure more than 7 days after the onset of the last symptomatic stroke) at 8 hospitals in Japan. This study included only PSE patients with a first-ever seizure and assessed their functional decline and mortality at 1 year. Functional decline was defined as an increase in modified Rankin Scale (mRS) score at 1 year compared with baseline, excluding death. The associations between the seizure recurrence and the outcomes were analyzed statistically.
Results: A total of 211 patients (median age of 75 years; median mRS score of 3) were identified. At 1 year, 50 patients (23.7%) experienced seizure recurrence. Regarding outcomes, 25 patients (11.8%) demonstrated functional decline and 20 (9.5%) had died. No known causes of death were directly related to recurrent seizures. Seizure recurrence was significantly associated with functional decline (odds ratio [OR] 2.96, 95% CI 1.25–7.03, p=0.01), even after

adjusting for potential confounders (adjusted OR 3.26, 95% CI 1.27–8.36, p=0.01), but not with mortality (OR 0.79, 95% CI 0.25–2.48, p=0.68). Moreover, there was a significant trend where patients with more recurrent seizures were more likely to have functional decline (8.7%, 20.6%, and 28.6% in none, 1, and 2 or more recurrent seizures, respectively; p=0.006).
Conclusion: One-year functional outcome and mortality of patients with PSE were poor. Seizure recurrence was significantly associated with functional outcome, but not with mortality. Further studies are needed to ascertain whether early and adequate antiseizure treatment can prevent the functional deterioration of patients with PSE.

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Cognitive impairment as a comorbidity of epilepsy in older adults: analysis of global and domain-specific cognitions

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Purpose: This study aimed to investigate the cognitive function and its impact factors among older adults with epilepsy.
Method: People with epilepsy and controls aged ≥50 years were recruited. The global and domain-specific cognitive functions were evaluated by a comprehensive neuropsychological battery, including Mini-Mental State Examination, Auditory Verbal Learning Test, Trail Making Test A and B, Conflicting Instructions Task, Modified Common Objects Sorting Test, and Stick Test. Clinical characteristics of epilepsy (i.e., seizure frequency, early/late onset, seizure type, and the number of anti-seizure medications [ASMs]) were obtained from medical records. Multiple linear regression model was used to explore the potential impact factors of the cognitive function among people with epilepsy.
Results: Ninety people with epilepsy and 110 controls without epilepsy completed the clinical interview. Older adults with epilepsy were more likely to be cognitive impairment compared to controls (56 [62.2%] vs. 28 [25.5%], $p < 0.001$). People with epilepsy performed worse on global cognition ($p < 0.001$), Memory ($p < 0.001$), Executive Function ($p < 0.001$), Language ($p < 0.001$), and Attention ($p = 0.031$) after adjusting for age, gender, education years, hypertension, diabetes, and heart diseases. Among older adults with epilepsy, age was negatively correlated with Memory ($\beta = -0.303$, $p = 0.029$), Executive Function ($\beta = -0.354$, $p = 0.008$), and Attention ($\beta = -0.558$, $p < 0.001$). Females performed better on Executive Function ($\beta = -0.350$, $p = 0.002$) than males. Education years had a positive correlation with global cognition ($\beta = 0.314$, $p = 0.004$). The number of ASMs was negatively correlated with Spatial Construction Function ($\beta = -0.272$, $p = 0.019$).
Conclusion: Cognitive impairment was a common condition concomitant with epilepsy. The number of ASMs may be a potential risk factor of cognitive impairment in older people with epilepsy.

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Sleep apnea, hypoxia, and late-onset epilepsy: the atherosclerosis risk in communities study

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Purpose: Sleep apnoea is associated with unexplained epilepsy in older adults in small studies. We sought to determine the relationship between sleep apnea and additional sleep characteristics and late-onset epilepsy, adjusting for comorbidities, using data from the large, prospective Atherosclerosis Risk in Communities (ARIC) Study cohort.
Method: We used Medicare claims to identify cases of late-onset epilepsy (LOE) in ARIC participants. We used polysomnography data from 1309 ARIC participants who also participated in the Sleep Heart Health Study in 1995-1998, and demographic and comorbidity data from ARIC. Later risk of LOE was evaluated using survival analysis with a competing risk of death. We also used survival analysis in 2672 ARIC participants to identify the association between self-reported obstructive sleep apnea (2011-2013), and the risk of subsequent LOE.
Results: Late-midlife oxygen desaturation to less than 80% during sleep was associated with subsequent development of LOE, adjusted subhazard ratio 3.28 (1.18-9.08), but the apnea-hypopnea index was not related. Participant report of diagnosis of sleep apnea in 2011-2013 was also associated with subsequent LOE, adjusted subhazard ratio 2.59 (1.24-5.39).
Conclusion: Sleep apnea and oxygen saturation nadir during sleep are associated with LOE, independently of hypertension and other comorbidities. These potentially modifiable risk factors could have large clinical implications for LOE.

Epilepsy in Resource-restricted Settings

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Epilepsy diagnostic gap in Nairobi informal settlements: findings from the epilepsy pathway innovation Africa (EPInA) study

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Purpose: Epilepsy diagnosis is a major challenge in Africa. In this study we estimated the epilepsy diagnostic gap among people living with epilepsy in two Nairobi urban informal settlements.
Method: Between October and December 2021, a total of 56425 people living in two Nairobi informal settlements (Viwandani and Korogocho) were screened for epilepsy at their households. Individuals that screened as potentially having epilepsy were referred for confirmation of diagnosis by a neurologist. We estimated the diagnostic gap as the proportion of people with active epilepsy who had not been previously diagnosed by a physician. Modified Poisson regression with a log link was used to determine associations between the diagnostic gap and socio-demographic characteristics of the participants. Prevalence ratios (PR) and 95% confidence intervals (CI) are reported.
Results: In total, 56425 individuals from 22536 households were screened, 1,126 were identified as probable epilepsy cases. Of these, 873 were assessed by a neurologist. 455 individuals were confirmed to have epilepsy of whom 349 (77%) were receiving this diagnosis for the first time. Factors associated with higher rates of being undiagnosed with epilepsy included being married compared to unmarried (PR=1.26; 95% CI=1.07-1.47), employed compared to unemployed (PR=1.22; 95% CI=1.02-1.46), being younger than 28 years compared to older (PR=1.24; 95% CI=1.08-1.41) and living in Viwandani (industrial area) compared to Korogocho (a relatively more stable population) (PR=1.23; 95% CI=1.07-1.42).
Conclusion: We have demonstrated that a wide diagnostic gap for epilepsy in Nairobi informal settlements exists. The higher gap among married and employed people may be because this group has fewer or less severe seizures but may also partly be explained by stigma, lack of awareness about epilepsy, cultural beliefs and perception coupled with limited capacity of primary healthcare workers to diagnose epilepsy. Training primary health care workers to diagnose epilepsy and increasing public awareness of epilepsy is required.

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Improving access to high-quality EEG for rural and urban patients in the U.S.'s largest governmental healthcare system: The Veterans Healthcare Administration (VHA) National TeleEEG program and Epilepsy Centers of Excellence (ECoEs)

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Purpose: Disparities in access to EEG and epilepsy specialist care exist within the United States. Number of epilepsy board-certified neurologists per U.S. state can vary from over 100 (e.g. California) to zero (e.g. Montana, Alaska). To improve access to specialized epilepsy and EEG services for the 6 million Veterans from 50 states who receive VHA healthcare annually, 16 geographically dispersed VHA ECoEs were created in 2009. Over the next 13 years, select ECoE hubs began providing asynchronous EEG services to underserved regions and improving ambulatory EEG access to centers without inpatient EEG capacity. The National VHA TeleEEG Program received dedicated federal funding in FY22 with the goal of expanding EEG access to underserved regions.
Method: Retrospective national cohort study of VHA EEG utilization over the past 12 fiscal years (FY) including VHA TeleEEG volume and cost of non-VHA based (out-of-network) EEG referrals.
Results: TeleEEG Hubs increased from 3 in FY13 (Portland, Boston, and Durham VHAs) to 6 in FY22 (Portland, Boston, Durham, Madison, Gainesville, and Baltimore VHAs). Spokes increased from 3 in FY13 to 22 in FY21 (10 active) and 14 active connections by FY23. Tele-EEG volume increased from 50 EEGs in FY13 to 896 in FY22. Ambulatory and Home EEG capacity increased from zero in FY11 to greater than 988 24hr studies in FY22. Since FY18, at least $5 million has been spent on non-VHA-performed, federally funded EEG studies.
Conclusion: The VHA National TeleEEG network increased access to EEG services across the VHA, expanding high-quality epilepsy care to resource-restricted regions of the US. National funding has allowed further expansion and modernization with aim of creating a centralized integrated VHA EEG Network. This network is the largest of its kind in U.S. and may serve as a model for teleEEG networks serving global health.

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EEG findings and its role in prognosis of post cardiac arrest hypoxic-ischaemic encephalopathy patients at a tertiary care centre – a prospective observational study

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Purpose: Cardiac arrest (CA) is a devastating event associated with very high mortality rates. In patients who are initially resuscitated, hypoxic-ischemic brain damage is the leading cause of morbidity and mortality and almost 80% of patients remain comatose for long. Prognostication in hypoxic–ischemic encephalopathy (HIE) is a particular challenge because decisions to withdraw life-sustaining therapies largely depend on predicted prognosis. Primary objective-To identify EEG findings as a prognostic marker and predictor of fatal outcome in post-cardiac arrest comatose patients.

Method: 67 post-cardiac arrest patients (due to primary cardiac cause) with hypoxic-ischemic brain injury were included in the study. The clinical, EEG and radiological findings were studied and follow-up on day 30 done to find out prognosis and survival with poor outcome defined as death or cerebral performance category score 3-5. EEGs were classified as benign, malignant and highly malignant based on American Clinical Neurophysiology Society (ACNS) guidelines 2016. EEG was considered as highly malignant when there was a suppression, suppression with continuous periodic discharges or burst-suppression with or without discharges.
Results: Out of 67 patients, 38 patients(56%) died on 30 days of follow-up. Highly malignant pattern was most commonly observed in 28(41.8%) patients. On association of EEG pattern with survival, patients with highly malignant pattern had fatal outcome in 78.6% cases which was statistically highly significant(p value 0.001). On multivariate analysis, highly malignant EEG with Odd's ratio of 7.438 (p value- 0.009), Glasgow coma scale (GCS) motor score ≤ 2 on day 3(p value- 0.027) and cardiac comorbidity(p value- 0.026), were statistically significant as markers of fatal outcome. Those with benign pattern had better survival (77.3%).
Conclusion: Our prospective observational study explains that a routine EEG study can help in prognosis of post-cardiac arrest hypoxic-ischaemic encephalopathy patients. An EEG finding of highly malignant character acted as an accurate prognostic marker for poor survival.

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The Role of Teleneurology in epilepsy care in sub-saharan Africa and the WHO Intersectoral Global Action Plan

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Purpose: The Intersectoral Global Action Plan (IGAP) 2022-2031 aims to increase access to epilepsy care in developing countries, mainly at the primary care level. A large proportion of people with epilepsy (PWE) live in Sub-Saharan Africa (SSA), two-thirds have no access to treatments, and more than 90% of PWE are managed by non-physician clinicians (NPC) with poor education in epilepsy. Education and training to SSA NPC and teleneurology can help bring care to SSA PWE. The purpose of this study is to report the results of education and training to NPC and its impact on PWE management in SSA.
Method: Disease Relief through Excellent and Advanced Means (DREAM) is a public health program in ten SSA countries. In Malawi and Central African Republic (CAR), DREAM follows 18836 patients. Thanks to the Global Health Telemedicine (GHT) platform, and with the support of the Italian Society of Neurology, the "Besta Neurologic Institute", and the "Mariani Foundation", voluntary European neurologists send their advice to NPC in Malawi and CAR DREAM centers (where 2 video-electroencephalograms were installed). Several remote education sessions and 12 in-person training courses were provided to local NPC in the last two years.
Results: Since the start of our program in 2020, the number of treated PWE increased and is now 1064 PWE - 5.6% of DREAM patients in Malawi and CAR. The median age is 19,8 years, 68,6% of patients have less than 18 years, and 11% are older than 40 years. In the last 2 years, the teleconsultations for epilepsy were 1617 (815 in 2022). A total of 267 electroencephalograms have been transmitted.
Conclusion: Teleneurology, coupled with education and training to local NPC, is an important tool to improve epilepsy care in SSA, hence to reach IGAP goals.

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A comparison of an epilepsy management smartphone application and remotely-reported EEG in newly-presenting epilepsy in the Democratic Republic of Congo

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Purpose: Hardly anyone in the Democratic Republic of Congo (DRC) has access to an epilepsy specialist. Local doctors lack the skills to manage epilepsy on their own, for example determining either whether *episodes* are epileptic or not, or whether the *epilepsy* is focal or generalised. There are two ways they can be helped– first, a smartphone application (app), with input from a remote specialist (Epilepsy Management Aid, [NetProphets Pvt, India]), and second, by EEG,. This paper compares these methods for the first time, in newly-presenting patients with possible epilepsy.
Method: ASLEK is the major epilepsy non-governmental organisation in DRC. ASLEK doctors and technicians had been previously trained in EEG recording by TeleEEG. EEGs were performed locally, and reported remotely by TeleEEG. A focal or generalised spike or sharp wave

abnormality was taken as indicating a focal or a generalised epilepsy respectively. Five local doctors were trained on the app. They sent the app-generated summary to remote specialists, who replied with management suggestions. Fifty consecutive patients were assessed, 10 from each doctor. A sample of 22 patients was evaluated by video consultation for clinical accuracy by a different epilepsy specialist.
Results: The app considered 45 episodes to be epileptic, with five uncertain, and 38 to have focal epilepsy, with 12 uncertain. EEG was abnormal in three out of 46, two focal and one generalised. Video consultation confirmed epilepsy in all 22 patients seen.
Conclusion: An epilepsy management app with a remote clinical opinion is effective at both episode diagnosis and epilepsy type diagnosis in newly-presenting epilepsy. A single interictal EEG is insensitive at determining whether someone has epilepsy or not, but may help determine epilepsy type, particularly if this is not obvious clinically.

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Paroxysmal slow wave events as a diagnostic biomarker for epilepsy: lessons from rural Zambia

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Purpose: Epilepsy is one of the most common chronic neurological disorders. It affects over 50 million people, 80% of whom live in low-income countries, where the diagnosis and treatment of epilepsy are often challenging due to the lack of neurologists, pharmacotherapies as well as awareness and stigma. EEG is an essential tool used for the diagnosis of epilepsy. However, in rural settings EEG interpretation is difficult and may be prone to errors. There is therefore a need for a reliable quantitative biomarker to aid in the diagnosis of epilepsy. Paroxysmal slow wave events (PSWEs) are transient slowing in cortical network activity that can be quantitatively measured with scalp EEG. PSWE occurrence was shown to be higher in patients with epilepsy (PWE) compared to controls. However, little is known about PSWE occurrence in non-treated patients with epilepsy, and the relationship between PSWE events to disease severity and drug resistance.
Method: In this study, 83 EEG recordings were analyzed from patients with epilepsy at the Kakumbi Rural Health Centre in Zambia were analyzed and compared to EEGs recorded from outpatients with and without epilepsy in the Temple University Cohort in the United States, and the University Hospital of Bonn Cohort in Germany. MATLAB scripts were used to analyze PSWE characteristics

Results: PSWE were more prevalent in patients with frequent seizures and in those under 12 years old. Percent recording time in PSWE in the temporal and partial EEG sensors was higher in untreated Zambia patients compared to treated patients in the Temple University Cohort.
Conclusion: This study further support the use of PSWE as a biomarker for epilepsy. We found that PSWE detailed characteristics vary with disease severity, duration, and treatment.

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Challenges and solutions for the establishment of an African antiepileptic drug pregnancy registry: a call to action

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Purpose: The North American Antiepileptic Drug Pregnancy Registry (ADPR) has evolved to a key tool in order to comprehend the side effects of antiepileptic drugs (AED) during pregnancy and reduce morbidity. AED used during pregnancy is not the same in Africa and Northern America.
Method: A review of the current body of literature with a focus on the antiepileptic drug pregnancy registry in Africa was conducted using multiple scientific online databases. Search terms included “antiepileptic drug pregnancy registry“, “Africa”, “low and middle income (LMIC)”, and other related terms as a starting point for future initiatives.
Results: It was found that more than 1.3 billion people residing in Africa lack any well-established antiepileptic drug pregnancy registry. The side effects of AED commonly used in Africa during pregnancy are not well understood. The exact burden of AED during pregnancy in Africa is still unknown. Although many successful, long-term, initiatives for international collaborations are published, well-established collaborations in order to analyze the side effects of AED during pregnancy in Africa are lacking.
Conclusion: Disparities in access to care for patients suffering from a wide range of diseases have been well-published but established solutions are still under investigation. Partnerships between medical societies, research centers, and medical facilities in LMIC and high-income countries (HIC) are making progress to better understand the burden of disease in LMIC and create context-specific solutions for practice in the LMIC setting. Collaboration between the International League Against Epilepsy, departments of Gynecology and Pediatrics of medical centers in Africa, non-profit organizations, the industry, as well as other interested groups, could be a meaningful strategical step for establishing an African Antiepileptic Drug Pregnancy Registry.

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Transcontinental algorithms in epilepsy: an epilepsy type algorithm developed in India works in Sudan

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Purpose: The effects of epilepsy are worse in lower-middle-income countries (LMICs) where most people with epilepsy live, and where most are untreated. Correct treatment depends on determining whether focal or generalised epilepsy is present. EEG and MRI are usually not available to help so an entirely clinical method is required. Reanalysis of a previous study of 503 patients from India, used Bayesian methods to derive an algorithm with 11 variables which had a diagnostic accuracy of 92.2%. We have applied this algorithm to an adult Sudanese cohort with epilepsy.
Method: There were 150 consecutive adult patients with known epilepsy type as defined by two neurologists who had access to clinical information and EEG and neuroimaging ("the gold standard"). We used seven of the 11 variables, together with their likelihood ratios, to calculate the probability of focal as opposed to generalised epilepsy in each patient and compared that to the "gold standard". Sensitivity, specificity, and accuracy were calculated.
Results: The mean age 28 years (range 17-49) and 53% were female. The accuracy was 92 %, with sensitivity of 99% and specificity of 91% for focal epilepsy. The majority of patients had probability scores either less than 0.1 (generalised) or greater than 0.9 (focaL).
Conclusion: The results confirm the high accuracy of this algorithm in determining epilepsy type. They confirm that, in a clinical condition like epilepsy where a history is crucial, results in one continent can be applied to another. This is especially important as untreated epilepsy and the epilepsy treatment gap is so widespread. The algorithm can be applied to individual patients giving a probability score which can determine the appropriate anti-seizure medication. It should give epilepsy-inexperienced doctors confidence in managing patients with epilepsy.

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The stigma context, social inequalities and knowledge gaps about epilepsy among Ayete People in Southwestern, Nigeria

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Purpose: Stigmatisation has contextual and cultural meanings that are constructed in such a way that explain why people would interpret the diseases differently. Previous studies have focused on the prevalence and the burden of epilepsy without enough discussion on how meanings in epilepsy influence the stigmatisation. This study explains meanings and stigmatisation in epilepsy cases and the healing-processes in Ayete.
Method: Structured questionnaires were administered to 250 randomly selected respondents. Key Informant Interviews with 4 Traditional Healers and In-depth Interviews with 5 Lay referrals (Significant others) of 5 People Living with Epilepsy (PWE) and 2 community members were examined in-line with how the illness has affected them and their lay refer-

rals. Qualitative data were elicited using participant-observation while quantitative data were analysed descriptively analysis.
Results: Epilepsy is generally called "*Warapa*", classified as humanly or god-inflicted. Ninety-seven percent agreed for humanly-inflicted while (3%) for godly-inflicted. FGDs further categories epilepsy manifestations into five namely: *Ogun-oru* (night-battle), *Gbare* (sudden-seizure), *Otiti* (sudden gradual push), *Waaku* (Come die) and *Warapa* (epilepsy). In Ayete, epilepsy meanings drive stigmatisation. Life histories of PWE revealed that they go through humiliation, discrimination, and stigmatisation. The stigmatisation process through IDI revealed castigation on the individual character, then goes to social impairment and finally to abomination of the body which could exist either as felt or enacted stigma, changing life-patterns of PWE from that of independence to dependence. From findings, 210 (84%) of 250 respondents cannot share the same cup or plates with an epileptic patient although 63% agreed that it is not contagious.
Conclusion: The meanings given to epilepsy influence the stigmatization and prevent the healing process. The traditional healers are on rescue mission but have not succeeded yet. However, we cannot dismiss their methods since the potency of their various medicine helped to some extent in overcoming epilepsy and adjusting to life.

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Epilepsy diagnostic accuracy by epilepsy-trained community health workers compared to community physicians: results from the BRIDGE non-inferiority cluster randomized clinical trial

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Purpose: The World Health Organization (WHO) and other health authorities have recommended task-shifting epilepsy care to community health workers (CHWs) to bridge the epilepsy treatment gap in low-resource areas of Africa, where the epilepsy treatment gap has been estimated at 67%-95%. However, methods for task-shifting epilepsy diagnosis have not be

extensively tested, and task-shifted epilepsy care has not been widely implemented. Bridging the Childhood Epilepsy Treatment Gap in Africa (BRIDGE) project includes a non-inferiority cluster randomized clinical trial (cRCT) of task-shifted epilepsy care to epilepsy-trained CHWs (TSC) compared to physician care ("enhanced usual care", EUC).
Method: Children who screened positive for possible epilepsy in three northern Nigerian cities, using a previously validated Hausa language epilepsy screening and seizure classification tool, underwent additional diagnostic evaluations. Children from neighborhoods randomized to receive TSC were evaluated by epilepsy-trained CHWs remotely supervised by physicians. Children from neighborhoods randomized to receive care by physicians, were referred to physicians for epilepsy diagnostic evaluations and epilepsy care ("enhanced usual care"). All children enrolled in the BRIDGE cRCT were evaluated by physicians with expertise in epilepsy, who were blinded as to whether children received diagnostic evaluations by CHWs or by physicians.
Results: 1768 children (TSC = 882; EUC=886) were initially diagnosed with previously untreated epilepsy and enrolled in the BRIDGE cRCT. 84 of 1768 children, 31 of 882 (3.5%) in TSC and 53 of 886 in EUC (6.0%) were determined to not have active epilepsy by blinded physician diagnostic evaluations. Non-epileptic diagnoses included febrile seizures only (EUC=15; TSC=4), non-epileptic movements among children with cerebral palsy (EUC=6; TSC=3), psychogenic or non-specified behavioral non-epileptic events (EUC=8; TSC=5), and neonatal seizures only (EUC=4; TSC=0).
Conclusion: Epilepsy diagnoses by epilepsy-trained CHWs was not less accurate than epilepsy diagnoses by physicians in the BRIDGE cRCT, after using an epilepsy screening tool in the local language.

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Follow-up of people with epilepsy in the Tibetan area

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Purpose: The clinical information on people with epilepsy (PWE) in the Tibetan area, which is located at a high altitude and has unique ethnic culture and backward economic conditions, is limited. Previously, we retrospectively analyzed the demographic data and clinical data of PWE admitted to the Ganzi Tibetan Autonomous Prefecture People's Hospital (Chen J et al. Front. Neurol. 9:891). In this study, we attempted to further provide follow-up information of those people and determine their medication compliance and long-term prognosis.
Method: We included consecutive patients with a diagnosis of epilepsy in the Ganzi Tibetan Autonomous Prefecture People's Hospital between January 2015 and January 2021. Demo-

graphic and clinical data of patients were retrieved by reviewing medical records. Then a neurologist followed up with the patients by telephone in December 2019 and December 2021 according to a structured questionnaire. The questionnaire mainly included demographic questions, questions about Tibetan medicine and drinking, and questions related to seizure frequency and adherence to antiseizure medications (ASMs). Data from the questionnaires and medical records were analyzed with descriptive statistics.
Results: Four hundred and four PWE were enrolled. Most patients were Tibetan (n=302, 74.8%) or Han Chinese (n=95, 23.5%). At the first follow-up, 19 (6.2%) participants had died and 105(36.5%) patients answered the questionnaire. Among them, 52 (49.5%) patients insisted on taking ASMs and 10 (9.5%) patients used Tibetan medicine. Eleven patients (10.5%) were still drinking. For seizure status, 21 (20.0%) patients had ongoing seizures. Thirty-six patients (8.9%) died at the second follow-up. Finally, 120 (32.6%) patients finished the questionnaire. Sixty-three (52.5%) of the surviving participants took ASMs and 38 (31.7%) patients still suffered from seizures.
Conclusion: Our data showed poorer compliance and higher mortality of PWE in the Tibetan area. Education of local primary doctors and patients may enable better management of epilepsy in this population.

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Can we move forward with SEEG electrode reprocessing? Method description, safety assessment, and cost-benefit analysis

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Purpose: Though the safety and benefits of stereo EEG electrodes are well established, but their use is limited in developing countries due to their high cost. Reprocessing these electrodes would be a low-cost solution. The primary aim of this study was to describe the reprocessing method for SEEG electrodes. We have compared the first-use electrodes with reprocessed electrodes, their intracranial bleeds rate, infection rate, and treatment cost to assess their safety, efficacy, and economic benefits.
Method: One hundred sixty-two patients who underwent SEEG electrode implantation were retrospectively analyzed. Patients with a minimum of twelve months of follow-up were included. Enzymatic ultrasonic wash and drying, chlorhexidine wash and drying, and vapourised hydrogen peroxide sterilization were the reprocessing steps. Electrodes lacking mechanical integrity and electrical fidelity were removed from reprocessing pool.
For this analysis, patients were segregated into three groups: N (Only first-use electrodes), NR (new and reprocessed electrodes), and R (Only reprocessed electrodes). From the patient electronic database, the neurological complications, intracranial bleeds, bacterial infections

(superficial and intracranial), and viral and prion diseases were collected. The cost of surgery and SEEG electrodes were compared across the groups.
Results: On average, 11 electrodes were implanted in these patients. There were 11 post-implantation intracranial bleed (N: 4; NR:2; R:5). The risk of neurological deficit per electrode was 0.001. The risk of bleeding was 6.7 % per patient. There were no bacterial, viral or prion infections in any group. Total surgery cost was $ 35801, $ 8845, $ 3894 in N, NR, R groups, respectively. SEEG electrodes cost was $14060 in N, $ 2868 in NR, and none for R group.
Conclusion: Our SEEG electrodes reprocessing method is safe for the invasive evaluation of epilepsy with no added bacterial, viral, or prion risk. Reprocessing of electrodes would make SEEG evaluation affordable in low-resource countries.

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Program implementation in a universal healthcare system: SPECT testing for children who are epilepsy surgical candidates in London, Ontario, Canada

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Purpose: Epilepsy surgery is the only cure for children with drug resistant focal epilepsy. When localization of the epileptogenic zone and/or lateralization is difficult, advanced diagnostic testing may be required. Children's Hospital, London Health Sciences Centre is designated as one of two pediatric regional epilepsy surgical centers in Ontario. However, diagnostic testing for surgical candidacy was limited to MRI, PEMU and PET. The purpose of this project was to determine if implementing a pediatric SPECT program was feasible and improved accessibility in a resource limited epilepsy surgery centre.
Method: In 2019, a quality improvement project was initiated and stakeholders from nuclear imaging, paediatric epilepsy, and inpatients were identified. Information was gathered and internal guidelines were created with the goal to admit 1 SPECT within the PEMU per month. Nuclear radiation safety education was built and provided to staff and online educational materials were created for children and their families. Well selected patients $\geq$ 5 years of age were chosen for the test and subsequently admitted for SPECT.
Results: In December 2020, the first pediatric SPECT patient was admitted. From December 2020 - May 2022, 15 SPECTS were completed, 11 females and 4 males. Successful injections were 60% (n=9). Out of the successful injections, 5 were localizing, resulting in 2 resective epilepsy surgeries. One to one nursing was initiated by the designated epilepsy program nurse and has extended to over 10 inpatient nurses educated and assisting with injections.
Conclusion: In conclusion, formalizing a SPECT program within a PEMU utilizing 1:1 care with nursing and specialist assists in completing successful injections. With education and training, engagement of nursing and fellows has grown allowing the team to expand and ease access to admitting children for SPECT. Further research is needed to see what other contributing factors are necessary for successful SPECT testing in resource limited settings.

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Strategies to optimize the surgical outcome of people with drug-resistant epilepsy and malformations of cortical development

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Purpose: Optimizing the surgical outcome of people with drug-resistant epilepsy and malformations of cortical development can be quite challenging. In this study, we report a large cohort of people with DRE and MCD encountered over a 10-year period at a single Institution analysing various types of MCD, their pre-surgical evaluation as well as the surgical strategies. These strategies may help in the management of people with DRE and MCD in other centres with similar socio-economic profile.
Method: Between April, 2011 and March, 2021, 496 people with drug resistant epilepsy underwent surgery at NIMHANS, Bangalore, India. Malformations of cortical development (MCD) as underlying substrate have been identified among 130 people with epilepsy (PWE). Different types of MCD, their pre-surgical evaluation, surgical strategy and outcome predictors have been studied.
Results: Cohort consists of 130 people with mean age at surgery being 17.61 ± 10.94 years. Mean age at seizure onset being 7.71 ± 7.39 years. The duration of epilepsy before surgery had a range of 1-32 years. Males constituted 61.5% of patients (n= 80). Mean Seizure score of the cohort was at 8.57 ± 1.34. Seventy three patients (62.9%) had FCD, 18 (15.5%) patients had DNET, and 4 patients (3.5%) had Ganglioglioma. At a follow up ranging from 1-12 years and mean (years) of 4.89 ± 2.80 years with median (IQR) of 4.41 (2.5 - 7.00) years, cohort had an Engel outcome class Ia, I, II, III and IV of 71.1%, 83.6%, 3.1%, 7.80% and 5.5 % respectively.
Conclusion: Three variables were found to influence the outcome towards favourable arm of Engel class Ia. These factors are histopathology of FCD with balloon cells, neoplastic variant of MCD i.e., DNET/GG and a younger age (less than eighteen years) of patient at surgery. Individual approach and patient-specific pre-surgical evaluation and surgical strategies are important determinant of outcome in centres in LMIC.

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Ictal single photon emission computed tomography (SPECT) in patients with focal aware seizure without ictal electroencephalographic changes: a single center experience

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Purpose: There is currently limited literature on the localization value of ictal SPECT tracer injection during patient-reported typical focal aware seizures (auras) that lack electrographic changes. One study reported that ictal SPECT studies in isolated auras lack reliability, with

concordant and correct localization with the seizure onset zone (SOZ) obtained in 5%, and lateralization in 35% of cases. We present a study in which tracer injection was administered for patient-reported typical focal aware seizures, where the subsequent analysis of ictal and interictal SPECT helped inform further management.
Method: We performed a retrospective review of cases who underwent ictal SPECT between July 2020 and June 2022 at the University of Kentucky hospital. Cases with radiotracer injection during patient-reported auras lacking electrographic changes were identified. Timing of injection from the onset of reported aura, hyperperfusion changes on ictal SPECT, and the outcome of imaging on further management of refractory epilepsy were noted.
Results: 20 patients underwent ictal SPECT, of which 7 met our inclusion criteria. None of the 7 cases had electrographic correlate with aura on scalp EEG. Time of tracer injection ranged from 1- 17 seconds following onset of aura. The ictal SPECT changes correctly localized the seizure onset zone in five patients. This was followed by intracranial monitoring and subsequent temporal lobectomy in three patients, interventricular ablation of epileptogenic focus in one patient, and Responsive Neurostimulation implant in one patient. One patient was managed medically, and one is ongoing pre-surgical evaluation.
Conclusion: Ictal SPECT with radiotracer injection during typical focal aware seizures (patient reported auras) without ictal electrographic changes is helpful in the localization of the seizure onset zone. Additionally, similar studies with larger sample size and outcome information are needed to assess accuracy of localization.

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A survey of the reality of epilepsy surgery in Latin-America

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Purpose: The classical concept is that epilepsy surgery (ES) is still underused in developing countries. Nevertheless, there are no accurate data concerning to the presence and practice of ES programs in Latin-America.
Method: An electronic survey was sent to Latin-American neurosurgeons and neurologists

from October 2022 to December 2022. Data were obtained from 80 ES programs in 18 countries. The survey focused on length of service, types of surgeries (curative, palliative and diagnostic) and population (pediatric or adult). Statistical analysis was performed with IBM SPSS Statistics 25.
Results: We registered a total of 25,333 procedures. Temporal lobe resection was the most frequent procedure (42,3%), followed by extratemporal resection (27,1%), callosotomy (8,7%), VNS (8,4%), hemispherectomy (5%), DBS (0,7%) and other procedures (0,2%). An invasive presurgical evaluation was performed in 7,5% of cases, including 827 patients with SEEG. The pediatric population was 36,3% of the cases.
The estimated ES per capita was between 1 per 207,571 habitants (Colombia) to 1 per 3,353,333 habitants (Honduras), with an overall Latin-American average of 1 case per 484,248 inhabitants.
Conclusion: Latin America performs all epilepsy surgical procedures except laser ablation or responsive cortical stimulation (RNS). The wide difference in the procedures per country depends on the amount of ES centers, resources, medical training, and governmental investment in health. There is an unmet need to improve ES access, especially in low-income Latin American countries and an evident need to standardize the access and complexity of epilepsy surgery procedures across the Latin American region which can be attained with increased awareness by stakeholders as well as development of educational resources and logistics which enable these techniques to be available to a broader range of patients, particularly during infancy.

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Subcortical grey matter structures in operated patients due to intractable temporal lobe epilepsy: a longitudinal volumetric analysis

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Purpose: Significant MR volumetric reduction of the cortical structures close to the hippocampus and other medial temporal structures in temporal lobe epilepsy (TLE) patients is known. However, MR volumetric abnormalities in TLE patients may extend beyond those structures. While successful TLE surgery might prevent ongoing neurodegeneration of wide temporal/extratemporal cortical zones, the effects on the atrophy of subcortical structures remain unknown.
Method: Thirty-six left and twenty-six right consecutive operated patients with TLE were included. Control groups consisted of 20 left and 18 right TLE patients who were waiting more than a year for epilepsy surgery and had at least two brain MRIs. All subjects underwent preoperative and postoperative MRI scans. Volumetric analysis based on a sagittal plane 3D T1-weighted (T1w) sequence was performed by FreeSurfer (https://surfer.nmr.mgh.harvard.

edu) software version 7.1.0. Statistical analysis was carried out in SPSS).
Results: Volume reductions of the left thalamus, nucleus caudatus, globus pallidus, amygdala and both, left and right nucleus accumbens were observed in the group of operated left TLE patients. Operated right TLE patients group demonstrated reduction of left and right thalamus, left and right amygdala, left and right nucleus accumbens, right putamen and globus pallidus volumes. A group of non-operated left TLE patients demonstrated volume reductions of the left and right thalamus, left nucleus caudatus and left nucleus accumbens through observational time. Only the left thalamus volumes were smaller in the group of non-operated right TLE patients in repeated MRI acquisitions.
Conclusion: Operated patients due to TLE show different patterns of subcortical grey matter structures atrophy. Atrophy of the left thalamus, left nucleus caudatus and left nucleus accumbens in left TLE patients continues despite epilepsy surgery. Operated right TLE patients demonstrated atrophy of numerous subcortical structures (left and right amygdala, left and right nucleus accumbens, right thalamus, right putamen and right globus pallidus) when compared to non-operated patients.

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Seizure induction in the intracranial epilepsy population

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Purpose: Inpatient video-EEG monitoring is performed to study seizures. It is desirable to shorten hospital stay in these patients for sake of efficiency and tolerability. Inability to record habitual seizures affects the ability to make post-implantation surgical plans. Various procedures are performed to increase the likelihood of seizure occurrence. We assessed whether sleep deprivation provokes seizures, how tapering of sodium channel or non-sodium channel drugs impacts seizure occurrence, and whether lobe of origin influences time of first seizure.
Method: Data from 231 adult patients above age 18 who underwent intracranial video-EEG monitoring at a single center from 2014 to 2021 was analyzed. Dates and times of seizures, medication types and doses, baseline seizure frequency, use of sleep deprivation, and lobe of seizure origin were collected. A Cox Proportional-Hazards model was used to analyze the time to seizure for patients that underwent various stimulation protocols, as well as for the patients that did not. The analysis was controlled for gender, age, baseline seizure frequency, and lobe of seizure onset.
Results: Partial and full stoppage of sodium channel drugs were associated with a significantly increased risk of seizure ($p=0.007$, $p<0.0001$), while only full stoppage of non-sodium channel drugs was associated with an increased risk of seizure ($p<0.0001$). As the number of seizures patients had during their stay increased, the risk for further seizures increased ($p=0.0001$).

Sleep deprivation did not increase risk of seizure within the next 24 hours. Patients with temporal lobe seizures had a significantly lower probability of seizure occurring (p=0.0005) within the first 8 hours of admission. Baseline seizure frequency did not affect seizure induction.
Conclusion: These findings suggest that tapering and stopping of sodium channel AEDs is more effective at inducing seizures than tapering non-sodium channel drugs. Sleep deprivation did not appear to be effective at inducing seizures.

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Coexistent extratemporal MRI lesions in patients with temporal lobe epilepsy and hippocampal sclerosis do not have impact on long-term seizure outcome after epilepsy surgery

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Purpose: High seizure freedom rates can be achieved postoperatively in patients with mesial TLE caused by unilateral hippocampal sclerosis (uHS). In some candidates, coexisting ipsilateral or contralateral extratemporal lesions (eTL) such as nonspecific gliosis or cortical defects are found on preoperative MRI. These patients are often thought to be less likely to achieve seizure freedom. The aim of this study was to evaluate the influence of eTL on long-term seizure outcome in patients with uHS and eTL compared to patients with uHS as sole pathology.
Method: 88 patients with complete long-term follow-up data (at least 2 years) were included. Patients with uHS alone formed group A (n=72), those with additional eTL on MRI formed group B (n=16). Seizure outcome was classified according to the ILAE classification.
Results: Gender distribution (male 58% vs. female 44%), mean age at epilepsy onset (6 years ± 12.6 vs. 15 years ± 15), and duration of epilepsy (23.6 years ± 14 vs. 20 years ± 15.7) show no significant difference between groups A and B. The mean follow-up (FU) was 3.2 years ± 2.4 in group A vs. 4.19 years ± 1.47 in group B and was not significantly different. The uHS in group B was more frequently located in the left hemisphere (87.5% vs. 47.7%, p=0.004). Subsequently, 83.3% of patients in group A were seizure free (ILAE class 1) after long-term FU, whereas 75% of patients in group B were seizure free. There was no significant difference in seizure outcome between the two groups.
Conclusion: In this study we were able to show that the presence of coexisting eTL on MRI in patients with TLE and uHS does not influence the probability of postoperative seizure freedom after epilepsy surgery. These results should be considered in the preoperative counseling of suitable and carefully selected candidates for resective epilepsy surgery.

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Clinical features of automatism and correlation with the seizure onset zones: a cluster analysis of 74 surgically treated cases

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Purpose: Localizing seizure onset zone (SOZ) according to semiologic features of automatism is challenging. We aimed to identify semiologic patterns that correlate to the anatomic origin of seizures with automatism.
Method: We assessed a total of 204 seizures from 74 patients with either oral or manual automatism. The location of the SOZ was determined using presurgical anatomo-electroclinical data (including stereo-EEG if performed), postsurgical brain MRI, and postoperative outcome (Engel's classification). Patients were divided into four subgroups according to the location of the SOZ: frontal, neocortical temporal, posterior and mesial temporal cortex. Eleven clinical features were combined into a multi-criteria scale, based on which the k-means analysis was then performed. Subsequently, the patterns of the semiologic clusters were correlated with the SOZ localizations.
Results: The clinical features were compared between the two examiners with a good inter-rater agreement (82.3%). Four semiologic patterns were identified (Figure 1). Cluster 1 was characterized by frequent aura, post-ictal confusion with a short delay of automatism, and correlated significantly with mesial temporal lobe epilepsy ($p = .017$). Cluster 2 was characterized by remarkable hyperkinetic movement with a moderate version. Cluster 3 included one-third of patients with frontal lobe epilepsy and was characterized by strong emotionality. Cluster 4 was characterized by strong contralateral dystonia with prominently short delay of automatism, and correlated significantly with neocortical temporal lobe epilepsy ($p = .011$). Besides, the SOZ localization of the four semiologic clusters were illustrated on the schematic plot (Figure 2).
Conclusion: In this study, the cluster analysis illustrated four clinical patterns of automatism characterized by various clinical features. Moreover, several correlations between semiology and SOZ localization were found. In terms of the clinical application, the accompanying symptoms of the four patterns could provide essential information in SOZ localization for focal seizures with automatism.

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De novo PNES after surgery in patients with refractory temporal lobe epilepsy (PR-TLE): high prevalence and possible influence on outcomes

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Purpose: The data on prevalence of psychogenic non-epileptic seizures (PNES) in patients

with refractory epilepsy after surgery is contradictory. We aimed to evaluate the prevalence of de novo PNES after surgery and their possible impact on surgery outcomes in PRTLE.
Method: Thirty-seven preoperative PNES-free PRTLE out of 108 patients who underwent a comprehensive presurgical evaluation (including video-EEG-monitoring) and surgery in Moscow from 2014 to 2021 were included. All patients were evaluated with the Mini International Neuropsychiatric Interview (M.I.N.I) v. 7.0.0 and Engel scale ≥ 1 year after surgery, and completed EpiTrack, QOLIE-31, and brEASI. All PRTLE with seizures underwent video-EEG-monitoring after surgery. Diagnosis of PNES was verified with video-EEG ictal recording. Mann-Whitney U-test and logistic regression were used for statistical analysis.
Results: Eight (22%) out of 37 had de novo PNES within the first year after surgery (5.9±3.6 months). Fourteen patients (37.8%) were diagnosed with psychiatric disorders (PD), mostly anxiety disorders and major depressive disorder. Nine of 14 had ≥ 2 PD. All patients with PNES had PD (100%) versus 6 out of 29 (20.7%) among patients without PNES. Having ≥ 2 PD was significantly associated with de novo PNES after surgery (OR=10.4, CI 95%=1.65-65.7, p<0.05). There were no age, gender and Engel scale differences between patients with and without PNES. PRTLE with PNES demonstrated worse quality of life (Q31, 43.7±8 vs. 68.4±14.7, p<0.001), cognitive functions (EpiTrack, 23±6.4 vs. 28.5±5.2, p<0.05), and anxiety level (brEASI, 11±6 vs. 5.8±5.3, p<0.05).
Conclusion: There was a high prevalence of de novo PNES after surgery in our cohort, especially in PRTLE with PD. De novo PNES were significantly associated with worse quality of life, cognitive functions and anxiety level after surgery. Timely diagnosis and appropriate management of PNES are important.

Funded by the Moscow Center for Healthcare Innovations, Grant №2412-45/22

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The intrinsic geometry of brain connectivity as a biomarker in epilepsy

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Purpose: Epilepsy is nowadays conceptualized as a network disease with functionally and/or structurally aberrant connections on virtually all spatial scales. Connectivity (network) analysis in epilepsy has provided valuable information on seizure onset, propagation and termination, and on the brain functional organization after resection surgery. The purpose of this work is to study such networks for patients undergoing brain epilepsy surgery in order to predict the outcome.
Method: We examined brain networks from 51 patients (estimated from T1-weighted structural MRI and diffusion-weighted MRI acquired before surgery, and from T1--weighted images after surgery). Pre/post-surgery networks were available in a public dataset associated to the study of Sinha et al, Neurology 2021. We embedded the pre- and post-surgery networks in an

hyperbolic space (Poincaré disk) and compared them with the hyperbolic metric to fully capture the rich structural organization change in brain connectivity induced by surgery. We incorporated connectivity information in a machine learning framework to predict patient-specific risk of seizure recurrence after surgery.
Results:
We found that hyperbolic geometries can represent patients brain networks and can unveil properties that could potentially result in robust biomarkers for surgery outcomes. Our method achieves an AUC of 0.865 +/- 0.003 in predicting successful seizure outcomes. The representation of brain networks in hyperbolic space can also identify regions of interest responsible or implicated in the surgery failure that could help to understand the unfavorable surgery outcomes for some patients.

Conclusion: In conclusion, non-Euclidean geometries seem to be well adapted to the representation of brain connectivity, especially in the study of epilepsy. This new representation of brain networks makes it possible to define new biomarkers, such as for the results of epilepsy surgery, and opens the door to work further using this new representation.

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Expedited epilepsy surgery and outcome measures of importance - patient/carer and clinician perspectives

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Purpose: Most epileptic children with focal cortical dysplasias (FCD) or long-term epilepsy-associated tumours (LEATs) progress to drug resistance, the point at which surgery is considered. Earlier surgical referral may reduce uncontrolled seizure activity on the developing brain, improving long-term cognitive outcomes. Designing a trial assessing expedited surgery efficacy requires input from patients, relatives, carers and clinicians to determine feasibility and outcome measures of importance. This study aimed to explore these perspectives.
Method: Online surveys were distributed through social media platforms, epilepsy charities and societies. Responses from 205 patients, parents and carers (61% from the UK and 26% from North America) and 51 UK-based clinicians were evaluated. The latter included paediatricians, paediatric neurologists and epilepsy specialist nurses. Data was collated from February to July 2022. Respondents answered questions exploring candidacy for epilepsy surgery, treatment outcomes and expedited surgical referral. Comparisons were explored between participant subgroups using Pearson's chi-squared test.
Results: 65% of patients and parents/carers would consider early surgery, with more parents/carers in favour compared to patients (71% vs 54%; p = 0.016). Views were largely similar

between UK and North American respondents. Among patients, caregivers and clinicians, seizure freedom, quality of life and seizure frequency were the most prioritised outcomes following surgery. 73% would consider early surgery before drug resistance develops, and 80% voiced support for the proposed trial. Paediatric neurologists and paediatricians did not differ in their views ($p > 0.05$).
Conclusion: The findings highlight that patients, parents, carers and clinicians generally support early epilepsy surgery for suitable candidates and would endorse a trial assessing this intervention. Concordance was displayed regarding outcomes these respondent subgroups value most highly following surgery. Understanding such shared priorities will facilitate future trial design that accounts for the preferences of those undergoing epilepsy surgery, their caregivers and the healthcare professionals delivering their care.

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Epilepsy surgery for drug-resistant epileptic spasms in children

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Purpose: Children with drug-resistant epileptic spasms may be surgical candidates when clinical spasms, EEG, and/or neuroimaging show laterality. The purpose of this study is to assess whether the presurgical evaluation predicts the outcome of the surgery.
Method: One hundred and five children underwent intracranial EEG monitoring (subdural grid or stereo-EEG) from June 2015 to August 2022. Eleven children (10%) had clusters of epileptic spasms as the primary seizure type. The clinical history, neurological examination, scalp-video-EEG, MRI, PET, MEG, surgical procedure, and pathology were analyzed.
Results: Seven out of 11 children had a history of infantile spasms (64%). MRI showed multiple tubers in the context of Tuberous Sclerosis Complex (TSC) in 2 children and subtle MRI abnormalities in the surgical hemisphere in 9. The mean age of intracranial EEG monitoring was 5.6 years (range: 2 to 10 years). Eight children underwent resective surgery, consisting of frontal lobectomy (2), multi-lobar resection (1), subtotal hemispherectomy (2), and functional hemispherectomy (3). Two children with TSC did not undergo resective surgery. One patient with normal PET has not yet undergone surgery. Three children with functional hemispherectomy had shorter seizure-free periods between infantile spasms and recurrence of epileptic spasms (quiet period) than the other children. One patient with frontal lobectomy had no history of infantile spasms, and the other had the most prolonged quiet period (8 years). When MRI, MEG, and PET were discordant or consistent with diffuse hemispheric epilepsy, subtotal or functional hemispherectomy was chosen. Pathological diagnoses were oligodendrogliosis (5), astrogliosis (1), oligodendrogliosis/astrogliosis (1), and filaminopathy (1). Post-surgery, 8 children are seizure-free with a mean follow-up of 32 months (range: 5 months to 7 years).
Conclusion: A careful review of the presurgical evaluation can predict the surgical procedure

and outcome in children with drug-resistant epileptic spasms.

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Resective vs disconnective and combined hemispherectomy for severe hemispheric intractable epilepsy – a meta-analysis

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Purpose: Hemispherectomy is the most promising treatment for patients with severe hemispheric intractable epilepsy. Several techniques for this surgical intervention have been established over the years and the choice of technique is currently mostly dependent on the surgeon`s experience with a specific approach. Techniques which are based on resecting large parts of the hemisphere as anatomical hemispherectomy or hemidecortication can be distinguished from more modern concepts in which the hemisphere is disconnected (as in transsylvian or in vertical hemispherectomy), as well as combined methods like functional hemispherectomy or periinsular hemispherotomy.
We aim to demonstrate whether the choice of the surgical technique moderates surgical outcome in patients with severe hemispheric intractable epilepsy, as measured by seizure freedom and the incidence of death after surgery.
Method: We extracted 1841 articles via a set of 8 keyword combinations from pubmed and Cochrane. Two independent experts selected 495 articles. We performed a meta-analysis for all studies and a pooled-data analysis for studies where information on individual patients was available.
Results: None of the retrieved studies were randomized. Disconnective surgery yielded a significantly higher proportion of seizure freedom (0.83) than resective (0.70, p=.003) or combined surgery (0.66, p<.001) for patients with at least 1 year follow up (N cases=1034). For death (N cases = 1090), resective surgery had the highest proportion of death within a year (0.08), significantly higher than disconnective surgery (0.018; p=.013) and combined surgical techniques (0.006; p<.001). Acute CNS infections were most common after disconnective surgery, while acute and chronic neurological complications and chronic hemorrhage/infarction were most common after resective surgery.
Conclusion: Modern, disconnective approaches are more effective than combined or resective approaches for treating patients with severe hemispheric intractable epilepsy. In addition, disconnective and combined surgical techniques are safer than resective approaches.

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EEG microstate analysis and source imaging can pinpoint the epileptogenic zone

before epilepsy surgery

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Purpose: Multiple non-invasive techniques are used to estimate the epileptogenic zone (EZ) before epilepsy surgery. Among them, conventional EEG is traditionally reviewed seeking seizures or interictal spikes. Advanced EEG analysis approaches, however, can unearth information without necessarily relying on human review.
EEG microstate analysis (EEG-MSA) parses the recording into quasi-stable "microstates" showing a unique topography of electric potentials over the scalp. Although EEG-MSA has been largely proposed to examine brain states, no study so far investigated the combined use of EEG-MSA and *electrical source imaging* (ESI) for the presurgical localization of the EZ.
Our purpose is to test the hypothesis that patients with drug-resistant epilepsy (DRE) present "epileptic" EEG microstates, whose source localization (via ESI) pinpoints the EZ before surgery.
Method: We analyzed 19-channel scalp EEG (2-minute) from 18 children who had successful epilepsy surgery (Engel 1) and defined the EZ as their resection. We parsed the EEG into *n* microstates (*n*=2-20) and identified the optimal *n* by analyzing their *global-explained-variance* (n=8).
We localized the cortical sources of each microstate by thresholding the ESI solution and identified "epileptic-microstates" when their main sources overlapped with the EZ (or were very proximal).
Results: In 14 patients (78% of the cohort), MSA identified at least one *epileptic-microstate*. In these cases:

- cortical activation during *epileptic-microstates* was higher inside than outside the EZ (*p*-value<0.01; Wilcoxon rank-sum);
- *epileptic-microstate* sources were mostly generated inside the EZ (overlap>50% or distance<25mm);
- *epileptic-microstates* most often occurred without interictal spikes.

Epileptic- and *non-epileptic-microstates* did not differ in the content of spikes in the EEG tracings (*p*-value=0.62).
Conclusion: This study demonstrates that EEG-MSA can pinpoint "epileptic-microstates" in children with DRE, which localize the EZ independently from the presence of interictal dis-

charges.
Our findings suggest that MSA and ESI may help estimate the EZ non-invasively using brief EEG recordings, augmenting the presurgical workup of children with DRE.

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Metabolic connectivity in drug resistant mesial temporal lobe epilepsy

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Purpose: The study investigated metabolic connectivity (MC) of patients with drug-resistant mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis (HS) compared to healthy controls (HC) based on 18F-fluorodeoxyglucose positron emission tomography (PET). The research focused on the metabolic network differences between left and right HS and correlated MC changes with postoperative outcomes.
Method: PET scans from 47 patients with unilateral MTLE with histopathologically proved HS and 25 HC were included in the study. All the patients underwent a standard anterior temporal lobectomy with a follow-up of more than 2 years. MC changes were compared between groups left, right HS, and HC. Subsequently, differences between the metabolic networks of seizure-free and nonseizure-free patients after surgery were analyzed. Network changes were correlated with the clinical characteristics of patients.
Results: The study showed widespread metabolic network changes in HS patients compared to HC. The MC changes were more evident in the right HS, particularly in the ipsilesional temporal lateral cortex. The unfavourable surgical outcome was found in patients with decreased MC within the network including both hippocampi and operculoinsular regions.
Conclusion: There are major differences in the metabolic networks of left and right HS, with more widespread changes in the right HS. The MC changes may help predict surgical outcomes in patients with HS.
An abnormal metabolic network comprising both hippocampi and operculoinsular regions may play role in surgery failure.

Supported by project nr. LX22NPO5107 (MEYS): Funded by European Union – Next Generation EU.
Supported by MH CZ – DRO (MMCI, 00209805).

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Epilepsy surgery in early infancy: a retrospective, multicenter study

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Purpose: Epilepsy has the highest incidence in the first year of life. About a third of these affected children develop a drug-resistant epilepsy (DRE) often resulting in a neurocognitive decline and developmental delay. While epilepsy surgery is currently the only curative therapeutic approach, there is a reluctance to operate on infants, out of fear of anesthesiologic and surgical complications. A recent meta-analysis showed that epilepsy surgery in the first six months of life can achieve excellent seizure control. However, robust data on surgical complications and postsurgical cognitive development are lacking.

Method: We performed a retrospective multicenter study and identified 15 infants who underwent epilepsy surgery in the first six months of life.

Results: Infants where operated at a median age of 134 days (IQR: 58, range 61-186). The most common cause of DRE was malformation of cortical development, and 87 % of patients underwent a hemispherotomy. Two thirds of infants required intraoperative red blood transfusions. Severe intraoperative complications occurred in two patients: one patient had severe intraoperative blood loss and a further infant died due to cardiovascular insufficiency. At a median follow-up of 1.5 years (IQR: 1.8), 57% of patients were seizure-free. Three patients required reoperation, resulting in 79% seizure-freedom. Anti-seizure medication (ASM) could be reduced in two-thirds of patients, and all patients showed cognitive improvement after surgery.

Conclusion: Our findings suggest that early epilepsy surgery can succeed in achieving good seizure control, ASM reduction, and cognitive improvement, but is not free of perioperative risks and should therefore be performed only at specialized centers

Specific consistency score (SCS) for epilepsy surgery candidates: a possible application in limited source circumstance without FDG-PET

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Purpose: Degree of indication for epilepsy surgery is conventionally determined by considering multiple factors, including FDG-PET. FDG-PET can be performed in limited numbers of facilities. We propose the Specific Consistency Score (SCS) for focal epilepsy as a simple score and investigated the degree of usefulness with and without FDG-PET.
Method: We retrospectively scored cases (n=131) presented to our institutional conference, excluding ones of generalized epilepsy, or ones who refused surgery. First, plausible epileptic focus was tentatively defined. When the non-invasive 8 findings (History of febrile seizures, Seizure semiology, MRI, FDG-PET, Ictal/Interictal EEG, and Neuropsychology) were consistent with the laterality and lobes of the estimated focus, points were added, and the total points were labeled as SCS. The association between SCS and 3 clinical parameters, i.e., (1) whether resection was performed, (2) lobar concordance between the estimated focus and the determined focus by intracranial EEG recordings, (3) postoperative seizure outcome, was examined by univariate and multivariate analysis. We also analyzed the association between SCS excluding FDG-PET data (SCS-woPET), in which MRI points were doubled instead of MRI and FDG-PET points, and the same 3 parameters.
Results: The mean age of the 131 cases were 33.6 years. The diagnoses were mesial temporal lobe epilepsy (n=56), frontal lobe epilepsy (n=28), and others (n=47). Univariate analysis revealed SCS was significantly higher in the (1) resected cases ($p<0.005$), (2) cases in which the focus determined by intracranial EEG matched the preoperative estimated focus ($p<0.005$), and (3) good postoperative seizure outcome group ($p<0.01$). Multivariate analysis revealed high AUC (> 0.84) for all 3 parameters. These univariate and multivariate analysis results were kept good level in the association between SCS-woPET and 3 parameters.
Conclusion: The SCS allowed a simple and useful evaluation of the indications for epilepsy resective surgery, and it may be also applicable in limited source circumstance without FDG-PET.

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Correspondence between scalp-EEG and SEEG seizure onset patterns in patients with MRI-negative focal drug-resistant epilepsies

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Purpose: In the pre-surgical evaluation of drug resistant focal epilepsy video-EEG analysis of seizure is crucial. Scalp seizure-onset pattern (SOP) helps to infer the SEEG ones, the underlying lesion and the depth of the EZ in patients with a visible MRI lesion (*Tanaka H. et al., 2018*). The aim of our study was to evaluate how the SOP on scalp EEG can estimate the SEEG one and guide SEEG planning in patients with negative MRI.
Method: We retrospectively analyzed 41 patients who underwent video-EEG followed by SEEG monitoring in our department. We identified 5 SOP on scalp EEG and 8 SOP on SEEG. As seizures were not recorded simultaneously on scalp and SEEG we matched the seizures following the same method used by Tanaka et al. for lesional epilepsies.
Results: A total number of 45 pairs of SOP were matched between scalp EEG and SEEG. We observed a statistically significant association between the SOP on scalp EEG and the SEEG one at the same delay from the seizure clinical onset on both modalities ($p = 0.003$). On scalp, a fast seizure-onset was associated with a superficial EZ ($p = 0.027$) and a specific pattern correlated with an underlying focal cortical dysplasia ($p = 0.027$).
Conclusion: Scalp EEG ictal pattern correlate with the underlying SEEG at the time of its visibility on scalp, reflecting sometimes more the propagation pattern than the onset one. Scalp SOP can suggest the depth of the EZ and the underlying etiology even in MRI negative epilepsies.

1165

Genetic diagnostics in pediatric epilepsy surgery

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Purpose: Presurgical evaluation of children does not include genetic diagnostics routinely to address a putative underlying genetic cause/predisposition. In our Pediatric Epilepsy Surgery Program, we proposed genetic diagnostics routinely and used this data for counseling. Here, we report our algorithm and demonstrate the obtained genetic data.
Method: We analyzed retrospectively the data of children with drug-resistant epilepsy (DRE) operated within the last four years at our center. Proposed genetic testing including chromosome analysis, CGH array, and (trio-)whole exome sequencing (WES). In some patients genetic testing was not performed due to lack of parental consent or other factors.
Results: We included 63 children (f27, m35) in the study. Genetic data was available from 41 patients (WES in 38). We identified 20 variants with an ACMG III-V in 17 children (11xIII, 1xIV, 8xV) in the following genes: *TSC* (n=2), *HUWE1, GRIN1, ASH1I, TRIO, KIF5C, CDON, EEF1A2,*

ANKD11, TGFBR2, ATN1, MECP2 (Rett syndrome, n=2), *COL4A2, JAK2, KCNQ2, CACNA1E, ATP1A2, Gli3.* Seizure freedom was not achieved through epilepsy surgery in 9/63 patients within an observation period of 27 months (range 4-62). Of these, 6/9 had abnormal genetic findings.
Conclusion: We propose genetic diagnostics in children and adolescents with DRE to be incorporated routinely in the presurgical evaluation for DRE. The results obtained in our program did not results in a change of the surgery indication, but rather supported the counseling of patients and families with respect to the chance of postoperative seizure freedom and the chance to wean off all antiseizure medications after epilepsy surgery.

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Post operative seizure outcomes in temporal lobe Focal cortical dysplasia

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Purpose: To evaluate the frequency of occurrence of various types of FCD in temporal lobe and compare post-operative seizure outcomes in them.
Method: A **retrospective observational** study done at a single centre- Comprehensive Epilepsy Care Centre at Seth GS Medical College and KEM Hospital, Mumbai. We used individual duplicate archived files containing pre-operative workup and post-operative follow-up. All temporal lobe operated cases with histopathologically proven Focal Cortical Dysplasia operated between May 2000 and January 2020 with at least 1 year follow-up data are included.
Results: A total of 154 operated cases of temporal lobe drug refractory epilepsy were included with histopathological diagnosis of focal cortical dysplasia. 139 (90.26%) cases had associated lesion with FCD. Associated lesions were mesial temporal sclerosis in 112 (72.72%), tumour in 23 (14.94%) and others in 5 (3.25%) cases. 1 patient was very unique with dual pathology (MTS with type Ia FCD as well as a separate type IIb FCD) in same temporal lobe. At the end of 1 year, overall 136 (88.31%) patients had ILAE class 1 seizure outcome. 3 patients got reoperated for recurrent seizure due to residual lesion and are seizure free since reoperation. At the end of 10 years, out of 59 patients, 40 had ILAE class 1 seizure outcome. 8 patients completed 15 years post operative follow up and 7 had ILAE class 1 seizure outcome. Out of 81 patients who underwent ECoG guided surgery, 75 (92.60%) patients have ILAE class 1 seizure outcome.
Conclusion: Most common FCD associated with temporal lobe is type III and Mesial temporal sclerosis is most common lesion in them. Surgery in type III FCD has better seizure outcome as compared to other types of FCD. ECoG guidance gives better seizure outcome in temporal lobe FCD surgery when compared to no ECoG guidance.

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Long-term surgical outcome and predictors in posterior cortex epilepsy

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Purpose: Posterior cortex epilepsy (PCE) is often debilitating with high rates of resistance. Surgical management is less frequent with poorer outcomes compared to other focal epilepsies. Seizure freedom rates have varied across the studies with paucity of data from the low middle income countries. We aimed to elucidate the long-term seizure outcome and its predictors in patients undergoing curative surgery for posterior cortex epilepsy at a comprehensive epilepsy care center in south India.
Method: A total of 191 patients who underwent curative surgery for refractory PCE between 2001-2019 with a minimum 1 year post operative follow up were included. Clinicoradiological and electrophysiological details were collected from a prospectively maintained cohort. Outcome was assessed using Engel score (I and II favorable; III and IV unfavorable) along with its predictors at last follow-up.
Results: 67.5 % were males (129/191). Gliosis was the most common substrate (51%). After a mean follow up of 14 years, seizure freedom (Engel class I) was observed in 63% of the patients with an additional 10% (Engel class II) having favorable outcome. Antiseizure medications (ASM) were withdrawn in 10%. Redo surgery was mandated in 7.3%. On bivariate analysis, <3 median number of ASM (p=0.022), concordant ictal onset (p=0.004), complete resection (p=0.000) were associated with favorable outcome. Residual lesion on MRI (p=0.00), acute post operative seizures (p=0.000) and interictal epileptiform discharges (IED) on serial post operative EEG (p=0.000) were associated with unfavorable outcome. On multivariate analysis, median number of (ASM) (p=0.054), degree of resection (p=0.002) acute post operative seizures (p=0.025) and presence of IED on EEG at 1 year (p=0.012) predicted the outcome.
Conclusion: Nearly three fourth cohort had a favorable surgical outcome. Surgery in PCE, hence, remains a valuable option, in carefully selected cases with good surgical expertise. Our experience from a distinct sociodemographic cohort with a large sample size is noteworthy

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Clinical and histopathological factors influencing seizure outcome after ganglioglioma surgery

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Purpose: Gangliogliomas (GG) are glioneural tumors causing refractory epilepsy, often early in life. Neurosurgical resection can control or even cure seizures. However, postoperative recurrence of the epileptic seizures can occur. CD34 and BRAF-V600E mutations are well described histopathological markers but their influence on clinical behavior remains debated. We aimed to analyze how these and clinical factors influence seizure outcomes after ganglioglioma surgery.
Method: We performed a retrospective analysis of patients with histologically diagnosed gangliogliomas and epileptic seizures treated at our center. Seizure outcomes are reported according to the ILAE classification. BRAF-V600E mutation status and CD34 were detected immunohistochemically.
Results: Sixty-one patients, median age 16.1 years (IQR 11.0-28.9) with a median follow-up time of 5.0 years were included. The majority of GG, 72.1%, were in the temporal lobe followed by frontal (11.5%) and parietal (9.8%) localization. One year after surgery, 41 patients (67.2%) had a seizure outcome graded as ILAE class Ia or I. Residual tumor tissue was suspected on MRI in 20 cases (32.8%) and a second operation was performed in 15 patients (24.6%) leading to 50 patients (82.0%) being seizure free at last follow-up. Fifty-nine GG were graded as WHO I and two were WHO II. A BRAF-V600E mutation was detected in 29 specimens (47.5%) and 56 specimens were CD34 positive (91.8%). Patients with BRAF had an earlier median onset of epilepsy (8.3 years vs. 15.2 years, p=0.020). Residual tumor was a strong predictor of early seizure recurrence. In patients with complete tumor removal, BRAF mutation remained a significant factor for shorter seizure free survival (p=0.022).
Conclusion: Resection of gangliogliomas can provide seizure control in a high percentage of patients. As previously described complete surgery confers a benefit to patients. BRAF mutation seems to increase the epileptogenicity of gangliogliomas and should be studied further as a predictor of seizure relapse.

1306

Surgical genomics: how genes impact surgical evaluation and surgical outcomes in drug-resistant epilepsy

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Purpose: Determine the role of genetics on surgical outcomes of patients with drug-resistant epilepsy (DRE)
Method: Retrospective, multicenter.
Inclusion criteria:

- Patients older than 18 years.
- Diagnosis of drug resistent epilepsy (DRE).
- Pathogenic or likely pathogenic variants matching the epilepsy phenotype.
- When surgery was done, 2 years of follow up.

Patients were divided into 3 groups: resective surgery, palliative surgery (vagus nerve stimulation, deep brain stimulation or callosotomy), or no surgery.
Good outcomes were classified as Engel I and II and poor outcomes as Engel III and IV.
Results:

- 154 patients were included, 36 had resective surgery.
- Twenty-nine patients with mTOR pathway variants underwent resective surgery and 12/29 (41%) had a good outcome.
- Patients with variants of ion channel function and synaptic transmission (n=42) were less likely to be offered a resective surgery and were more commonly found in the group who received palliative surgery ($p<0.001$)
- Seven patients with variants other than mTOR pathway underwent resective surgery, with five (2 with *SCN1B*, 1 with *KCNA2*, 1 with *KCNH2*, and 1 with *PCDH19*) presenting with good outcome and two (1 with *CHD2*, and 1 with *SCN1A*) with poor outcomes.
- Fifty-two patients underwent palliative surgery (Vagus Nerve Stimulator, Deep Brain Stimulator or Callosotomy), with 62% of them being responders (>50% reduction of seizures)

Conclusion:

- Patients with mutations in ion channels were less likely to have resective surgery compared to those with mTOR mutations.
- Despite that, selected patients with monoallelic *SCN1B*, *KCNA2, KCNH2, PCDH19* pathogenic variants had good outcomes after resective procedures.
- By understanding the implications of genetic abnormalities on surgical investigation

and outcome, genomic findings can be incorporated as a prediction tool for evaluating surgical candidacy, along with additional investigations.

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The diagnostic value of ictal SPECT – a retrospective, semiquantitative monocenter study

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Purpose: Ictal single photon emission computed tomography (SPECT) can be used as an advanced diagnostic modality to detect the seizure onset zone in the presurgical evaluation of people with epilepsy. In addition to visual assessment (VSA) of ictal and interictal SPECT images, postprocessing methods such as ictal-interictal SPECT analysis using SPM (ISAS) can visualize regional ictal blood flow differences. We aimed to evaluate and differentiate the diagnostic value of VSA and ISAS in the Bonn cohort.
Method: We included 161 people with epilepsy who underwent presurgical evaluation at the University Hospital Bonn between 2008 and 2020 and received ictal and interictal SPECT and ISAS. We retrospectively assigned SPECT findings to one of five categories according to their degree of concordance with the clinical focus hypothesis.
Results: Seizure onset zones could be identified more likely on a sublobar concordance level by ISAS than by VSA (31% vs. 19% of cases; OR = 1.88; 95% CI [1.04, 3.42]; p = 0.03). Both VSA and ISAS more often localized a temporal seizure onset zone than an extratemporal one. Neither VSA nor ISAS findings were predicted by the latency between seizure onset and tracer injection (p = 0.75). In people who underwent successful epilepsy surgery, VSA and ISAS indicated the correct resection site in 54% of individuals, while MRI and EEG showed the correct resection localization in 96% and 33 % of individuals, respectively. It was more likely to become seizure-free after epilepsy surgery if ISAS or VSA had been successful. There was no MR-negative case with successful surgery, indicating that ictal SPECT is more useful for confirmation than for localization.
Conclusion: The results of the most extensive clinical study of ictal SPECT to date allow an assessment of the diagnostic value of this elaborate examination and emphasize the importance of postprocessing routines.

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Ictal testing in the video telemetry unit: Is it possible and does it add value? Audit of the ILAE Ictal testing battery in a tertiary video telemetry unit

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Purpose: Analysis of seizure semiology during video telemetry (VT) can improve lateralisation and localisation in epilepsy, and aid decision-making during epilepsy surgery evaluation (Foldvary-Schaefer N, Unnwongse K Epilepsy & Behaviour 2011;20:160-166, Elwan Seizure 2018;61:203-208). An ictal testing battery (ITB) was developed by the ILAE European Task Force in 2016 (Beniczky S et al Epilepsia 2016;57(9):1363-1368). We aimed to evaluate adherence to the ITB in our unit and assess any additional benefits.
Method: We performed a retrospective analysis of patients admitted for VT (intracranial, diagnostic and pre-surgical admissions) over a 2-month period from March to April 2019. 24 studies/patients were identified. The first three events of each seizure type in each patient were reviewed (106 seizures). The ITB was divided into ten parameters for analysis. Video-EEG and VT reports were reviewed to evaluate seizure attendance by nursing staff, safety measures instituted, and adherence to the ITB.
Results: 93/106 (87.74%) seizures were attended and 85/106 (80.19%) were subsequently assessed with the ITB. Oxygen was administered and bed rails raised in all seven focal to bilateral tonic clonic seizures. The first five ITB parameters were successfully completed in over 60% of seizures: responsiveness 98.82% (84/85); aura description 91.76% (78/85); orientation 82.35% (70/85); verbal/visual commands 75.29% (64/85); object naming 65.88% (56/85). Subsequent parameters were completed in less than 50% of seizures: reading/writing 43.53% (37/85), counting 44.71% (38/85); verbal memory 56.47% (48/85); visual memory 11.76% (10/85), motor power 29.41% (25/85). 35 lateralising or localising signs were captured and 7/35 (20.00%) were elicited using the ITB.
Conclusion: Seizure recognition and safety management were performed well. Half of ITB parameters were tested in > 60% of seizures, and 1 in 5 lateralising or localising signs were identified using the ITB. This confirms ictal assessment is feasible in an inpatient VT unit and can make an important contribution to epilepsy surgery evaluation.

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What is the best SEEG biomarker for predicting surgical outcome ?

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Purpose: Stereoelectroencephalography (SEEG) is the reference method in presurgical exploration of drug-resistant focal epilepsy. Prognosticating surgery on an individual level is difficult due to the great variability in clinical assessment. Quantification of the epileptogenic network thus becomes crucial to guide surgical decision. We compared the performances of ictal (Epileptogenicity Index, EI, Connectivity EI, cEI), interictal (spikes, HFO) and combined (spikes x EI, spikes x cEI, spikes x HFO) SEEG biomarkers in predicting surgical outcome and searched for prognostic factors based on SEEG-signal quantification.
Method: 53 patients with drug-resistant focal epilepsy who underwent SEEG and surgery were included. We compared the regions identified as epileptogenic by different SEEG biomarkers (EZ_q) against the visual analysis (EZ_c) using precision-recall. EZ threshold for each marker was defined using F0.5 vs EZc in seizure-free patients. Correlation between the EZc or EZq resection rates and surgical prognosis as well as between the EZ extent and clinical variables were analyzed.
Results: Spikes x EI and the EI showed the best precision against EZ_c (0.74; 0.70), followed by Spikes x cEI and the cEI, whereas Spikes, HFO and Spikes x HFO showed lower precision. Recall was highest for the cEI and combined biomarkers (0.46-0.41). The EZ resection rates were greater in seizure-free than in not seizure-free patients for the EZq defined by ictal biomarkers. The same trend but not significant was observed for the EZc and the combined markers but not for the interictal markers. The number of epileptogenic regions quantified by different biomarkers or visually defined did not correlate with the duration of epilepsy, nor with the surgical prognosis. The EZq was more extended in MRI-negative than in lesional cases.
Conclusion: Combining ictal and interictal epileptogenicity markers improves EZ detection accuracy. Surgical prognosis correlated to the resection rates for the EZ defined by ictal markers but not to the EZ extent.

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Mosaic variants detectable in blood extend the clinico-genetic spectrum of *GLI3*-related hypothalamic hamartoma

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tute for Genomic Medicine, Columbia University, New York, United States, [9]Eshelman School of Pharmacy, Division of Pharmacotherapy and Experimental Therapeutics, and Department of Genetics, University of North Carolina, Chapel Hill, United States

Purpose: Hypothalamic hamartoma (HH) is a benign lesion of the hypothalamus associated with syndromic and isolated clinical presentations. Pathogenic variants in *GLI3* are the most frequently identified genetic cause for both syndromic and isolated HH. The most well recognised, Pallister-Hall syndrome (PHS), is a rare developmental condition characterized by HH and mesoaxial polydactyly. Most individuals with PHS have germline variants in *GLI3* but a minority of individuals remain unresolved on routine clinical genetic testing. Individuals with non-syndromic HH typically present with a severe epileptic encephalopathy, and have also been found to have *GLI3* variants however in these cases the variants all arose post-zygotically, are somatic mosaic, and restricted to HH tissue. The clinical and genetic aetiology of PHS and non-syndromic HH have rendered these two *GLI3*-related disorders separate clinical entities.
Method: High depth exome sequencing and droplet digital PCR were employed to detect mosaicism of sonic hedgehog pathway or cilia genes in unsolved patients with PHS or non-syndromic HH.
Results: Genetic analysis revealed 3/26 (~11%) individuals with HH were mosaic for pathogenic *GLI3* nonsense or frameshift variants in blood. The first to be reported with mosaic *GLI3* in blood, one of these individuals had a clinical diagnosis of PHS, and two had non-syndromic HH, demonstrating the existence of a clinico-molecular spectrum between these two entities.
Conclusion: Our findings extend the spectrum of *GLI3* variants associated with HH and expand the genetic mechanisms underlying these two HH-related disorders. Increasing the diagnostic yield of PHS and non-syndromic HH has significant clinical and genetic counselling implications for individuals with HH. More broadly, our findings support the pursuit of causative mosaic variants that may be unrecognised in peripheral tissues of unsolved individuals with other Mendelian neurological disorders.

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Blockchain and artificial intelligence-enabled stratified trial system (BESTS) - A patient driven platform that leverages health data to accelerate clinical trial recruitment for epilepsy precision therapies

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Purpose: Precision medicine in epilepsy aims to provide individual treatment strategies for patients, often on the basis of an identified underlying monogenic cause. With accelerating genomic discovery, the number of potential targets that might enable a precision approach is rising. Clinical trials, an essential step in therapeutic development, need to become more personalised and stratified. However, recruitment continues to be a barrier for trial sponsors, clinical research teams and patients. This challenge can be met by connecting patients to trials via their clinical and genomic data. Here we present BESTS - a cloud-based platform developed for collaborative use by patients, healthcare providers (HCPs) and clinical research organisations. It allows patients to be matched to trials while retaining complete control and ownership of their data.
Method: User-centred design encompassing requirements engineering and prototyping was applied. Twenty-five participants representing HCPs and patients engaged in delphi interviews and ethnographic fieldwork to inform value proposition and user-requirements. Requirements were translated into mock-up designs to optimise platform layout. A clinical dataset, aligning with ILAE classification, was identified for trial-matching and includes epilepsy type, syndrome, seizures, aetiologies, current and prior ASMs and comorbidities. A bioinformatics pipeline that facilitates automatic re-analysis of sequences was built and deployed. Dynamic consent, enabled by blockchain technology, was developed to allow patients decide what data they would like to share.
Results: BESTS value propositions for patients includes greater control around their data, personalised trial-matching, contributing to research that benefits the wider population and access to genetic sequencing. Value propositions for HCPs includes identification of patients for trials and the potential to demonstrate suitability as a trial site.
Conclusion: Embedding user perspectives in the development of BESTS enables its real-world application. Fears around AI and Blockchain can be offset through transparency and informed consent. Accelerating trial recruitment will facilitate a faster introduction of treatments into care-pathways.

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Seizures in neurodegeneration with brain iron accumulation in a South Indian cohort

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Purpose: To investigate the frequency of seizures in Neurodegeneration with brain iron accumulation (NBIA) disorders in a South Indian cohort and to determine associated features.
Method: 25 patients from a single center in South India, with extra pyramidal features, spasticity, seizures and neuropsychiatric abnormalities in varying combinations with MRI evidence of iron deposition were included. Ancillary investigations including serum ceruloplasmin,

ferritin, blood sugar, smear for acanthocytes, fundus examination, neuropsychological assessment, electroencephalogram, and nerve conduction study were done according to the clinical presentation. Clinical exome /target gene sequencing for NBIA was done.
Results: 17/25 patients were males with age of onset ranging from 2-63 years (23.94±17.71). 9 were consanguineous born and 6 had a positive family history. Seizure was the first symptom in 4 patients (one had status epilepticus).Over the course total 9 (36%) patients had seizures. Other manifestations included dystonia (21), parkinsonism (10), ataxia(4), myoclonus (2), chorea (1), hand stereotypies (1). Oculomotor abnormalities (the most common associated feature) included slow saccades (16), oculomotor apraxia (2) and eyelid opening apraxia (1). Neuropsychiatric symptoms (8), pyramidal signs (4), optic disc pallor (3), and retinal pigmentary degeneration (1) were also noted. All had iron deposition in globus pallidus, detected on susceptibility weighted images (SWI) with additional SN (9), red nucleus (9) or combined RN, DN and striatum (3). Of the 9/25 NBIA patients (36%) with seizures mutations were detected in *PLA2G6* (4), *PANK2* (2), *WDR45* (1) and *CoSY* (1). 1 tested negative on NBIA targeted gene sequencing. 6 had generalized, 2 had focal seizures while 1 presented with status epilepticus. EEG showed generalized or central discharges.
Conclusion: *PLA2G6* associated neurodegeneration (PLAN) was the most common NBIA which presented with seizures followed by BPAN, PKAN and CoPAN. Associated eye movement abnormalities and dystonia help in NBIA identification when patients present with epilepsy.

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Exploring the genetic landscape of diphtheria, tetanus and pertussis vaccination-associated seizures or subsequent epilepsies

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Purpose: Diphtheria, Tetanus, and whole-cell Pertussis (DTwP) vaccination-associated seizures form the commonest type of serious adverse event following immunization in India and are an important reason for vaccine hesitancy. Our study explored the genetic explanation of DTwP vaccination-associated seizures or subsequent epilepsies.
Method: Between March 2017 and March 2019, we screened 67 children with DTwP vaccination-associated seizures or subsequent epilepsies, and of those, we studied 54 without prior seizures or neurodevelopmental deficits. Our study design was cross-sectional with a 1-year follow-up. We performed clinical exome sequencing focused on 157 epilepsy-associated genes and MLPA of the *SCN1A* gene. We applied the Vineland Social Maturity Scale for neurodevelopmental assessment at follow-up.
Results: Of 54 children enrolled and underwent genetic testing (median age 37.5 months), diagnosis at enrolment: epilepsy 29, febrile seizure 21, and febrile seizure-plus 4), we found 33 pathogenic variants of 12 genes. Of 33 variants, 13 (39%) were novel. Most pathogenic vari-

ants were found in *SCN1A* gene (n = 21/33; 64%), *SCN8A* in 2 children, and 10 children had one variant in *CDKL5*, *DEPDC5*, *GNAO1*, *KCNA2*, *KCNT1*, *KCNQ2*, *NPRL3*, *PCDH19*, *RHOBTB2*, and *SLC2A1*. Five or more seizures (odds ratio [OR] = 5.3, confidence interval [CI]: 1.6–18.4, p = 0.006), drug-resistant epilepsy (OR = 9.8, 95% CI: 2.6–30.7, p = 0.001) and neurodevelopmental impairment (social quotient < 70) (OR = 5.6, 95% CI: 1.65–17.6, p = 0.006) were significant predictors of genetic diagnosis.
Conclusion: Our study provides proof-of-concept for genetic aetiology in children with DTwP vaccination-associated seizures or subsequent epilepsies and has important implications for vaccination policies in developing countries.

Funding: International Pediatric Association Foundation and Indian Council of Medical Research, New Delhi, India.

Encore abstract: Paper published: Exploring the genetic landscape of diphtheria, tetanus and pertussis vaccination-associated seizures or subsequent epilepsies. The Lancet Regional Health-Southeast Asia. 2023 Jan 1;8:100094. DOI: https://doi.org/10.1016/j.lansea.2022.100094

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Development of an outcome prediction model for patients with monogenic epilepsy

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Purpose: Genetic and phenotypic heterogeneity are crucial issues for epilepsies with a genetic aetiology. The aim of this study is to verify the reliability of a Machine Learning (ML) approach in predicting the prognosis in patients with genetic epilepsy to improve genetic counselling and clinical management.
Method: We collected data from 253 patients with monogenic epilepsies. The following features were collected: age at onset, type of seizures, developmental delay, neuropsychiatric disorders, movement disorders, family history. Categories of outcomes were identified, based on clinical features at follow-up. A Chi2 statistical test and several Artificial Neural Networks (ANNs) were implemented.
Results: A statistically significant correlation was found between outcome and age at seizure onset, developmental delay, behavioural disturbances, family history, and movement disorders at disease onset. Considering all features, the ANNs provided a mean level of accuracy of 78.9% in predicting the outcome that increased to 86.2% using only the statistically significant

features.
Conclusion: We demonstrated the reliability of a ML approach in predicting outcome starting from clinical features at epilepsy onset. A future integration with other parameters (i.e. EEG features, specific genotypes) and a validation of the model in other paediatric cohort will be fundamental to increase the applicability of predictive model in clinical practice.

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Risk-conferring *HLA* variants in an epilepsy cohort: benefits of multifaceted use of whole genome sequencing in clinical practice

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Purpose: Whole genome sequencing is increasingly used in healthcare, particularly for diagnostics. However, its clinically multifaceted potential for individually-customised diagnostic and therapeutic care remains largely unexploited. We utilised existing whole genome sequencing data to screen for pharmacogenomic risk factors related to antiseizure medication-induced cutaneous adverse drug reactions (cADRs), such as *HLA-B*15:02*, *HLA-A*31:01* variants.
Method: Genotyping results, generated from the Genomics England UK 100,000 Genomes Project primarily for identification of disease-causing variants, were used to additionally screen for relevant *HLA* variants and other pharmacogenomic variants. Medical records were retrospectively reviewed for clinical and cADR phenotypes for *HLA* variant carriers. Descriptive statistics and the chi square test were used to analyse phenotype/genotype data for *HLA* carriers and compare frequencies of additional pharmacogenomic variants between *HLA* carriers with and without cADRs, respectively.
Results: 1043 people with epilepsy were included. Four *HLA-B*15:02* and 86 *HLA-A*31:01* carriers were identified. One out of the four identified *HLA-B*15:02* carriers had suffered antiseizure medication-induced cADRs; the point prevalence of cADRs was 16.9% for *HLA-A*31:01* carriers of European origin (*n*=46) and 14.5% for *HLA-A*31:01* carriers irrespective of ethnicity (*n*=83).
Conclusion: Comprehensive utilisation of genetic data spreads beyond the search for causal variants alone and can be extended to additional clinical benefits such as identifying pharmacogenomic biomarkers which can guide pharmacotherapy for genetically-susceptible individ-

uals.

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Novel genotype-phenotype correlations in GABRB1-related disorders

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Purpose: Pathogenic variants in genes encoding $GABA_A$ receptor subunits are associated with a spectrum of epilepsy syndromes. Here, we assessed phenotypes and functional properties associated with *GABRB1* variants.
Method: Individuals carrying a *GABRB1* variant were recruited through an international collaboration. Clinical information was collected using a standardized sheet. Functional studies on the mutant *GABRB1* subunits were performed by two-electrode voltage-clamp recording from Xenopus oocytes using the Roboocyte2®.
Results: Eleven persons carrying ten different (likely) pathogenic *GABRB1* variants were included, ten of which occurred *de novo*. Ten had epilepsy. Age at seizure onset ranged from 15 days to 10 years (median: 3.5 months). Seven had a developmental and epileptic encephalopathy (5 EIDEE, 1 EIMFS, 1 IESS), 1 GEFS+, and 2 Epilepsy with Myoclonic Atonic seizures. One had ID without epilepsy. Ketogenic diet led to >90% seizure reduction in two (1 GEFS+, 1 EMA) of four patients. All severely affected patients carried variants located in the pore domain.
Functional characterization showed *GABRB1* variants have loss-of-function (LoF, 2/10) or gain-of-function (GoF, 4/10) effects (analysis ongoing for remaining four). GoF invariably leads to syndromes associated with ID, while LoF can lead to both severe and milder phenotypes. Age at seizure onset does not distinguish between LOF and GOF (median LoF/GoF: 2/3.5 months). Profound ID is seen with both LoF and GoF, while mild/no ID seems to be associated with LoF. Dysmorphic features and progressive cortical atrophy were only noted in patients with GoF variants.
Conclusion: *GABRB1* pathogenic variants lead to various syndromes with or without epilepsy and/or ID. In line with other GABR genes, GoF variants lead to severe phenotypes, tend to cluster in the pore domain, and are possibly associated with EIMFS, dysmorphism and progressive cortical atrophy. LoF variants lead to mild and severe phenotypes, are possibly associated with generalized epilepsy, and are distributed among the gene.

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Joint analysis of multiple trio genomic datasets for the discovery of novel dominant epilepsy genes

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Purpose: The epileptic encephalopathies (EEs) and epilepsy with intellectual disability (ID) are groups of epilepsy characterized by refractory seizures and developmental regression. Both groups have been shown to have underlying monogenic causes, often due to dominant de-novo variants. However, despite state-of-the-art testing, a significant proportion of people with epilepsy with ID and EE do not receive a molecular diagnosis, suggesting there are additional, yet-to-be-identified genetic causes of these epilepsies. We set out to identify novel epilepsy with ID and EE genes by centralizing genetic trios datasets using whole-exome and genome sequencing technology (WES/WGS).
Method: For inclusion in this study, the participants must have provided consent for gene discovery research, have clinical phenotypes based on HPO terms with EE or epilepsy with ID, and have trio samples of WGS or WES available. Trio-based WES/WGS were from the FutureNeuro Research Centre (141 trios), the Epilepsy Genetics Initiative (29 trios), Epi4K/EPGP (337 trios), Undiagnosed Diseases Network (9 trios,1 quad), CSER (21 trios, 1 quad) and the UK 100,000 Genomes Project (269 trios). GATK4.2.0 pipeline was used for the variant calling steps. Statistical model using denovolyzeR were utilized to identify genes with a significant excess of de-novo variants (DNVs).
Results: A total of 806 trios and 2 quads were included in the final analysis. We identified 23 genes with a significant excess of DNVs and observed them in more than one unrelated patient, of which 19 were established monogenic causes of epilepsies. Among the potentially novel genes, the predicted damaging MAST4 variants are observed in three unrelated patients. All MAST4 patients had epilepsy and a similar developmental phenotype.
Conclusion: Combining genetic and phenotypic data, we report the significant enrichment of de-novo variants within our combined collection of over 2,000 individuals who underwent WES/WGS. We implicate de novo variants in MAST4 as a cause of epilepsy with ID.

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Biallelic and monoallelic ACTL6B variants lead to a wide spectrum of developmen-

tal and/or epileptic encephalopathy with autistic features and movement disorders

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Purpose: Biallelic pathogenic variants in *ACTL6B,* encoding for a subunit of the nBAF complex, have been associated with a severe early infantile epileptic encephalopathy. Additionally, de novo missense mutations at specific loci have been linked to a different neurodevelopmental disorder characterized by intellectual disability and severe speech and ambulation deficits. Although the function of the protein/complex in neuronal development has been well characterized, particularly since the identification of *ACTL6B* as a disease gene, there is still no comprehensive study describing the phenotypic spectrum associated with *ACTL6B* variants and the epileptic features associated with the disorder.
Method: The affected individuals were identified through data sharing with collaborators and screening databases of several diagnostic and research genetic laboratories worldwide. Detailed clinical data and family history were collected. Where available, electroencephalogram (EEG) recordings, clinical photos and brain MRI scans were reviewed and analysed systematically by a group of epileptologists, dysmorphologists and neuroradiologists.
Results: Here, we outline the characteristics and phenotypic spectrum of *ACTL6B*-related disorder in 70 patients from 60 unrelated families, including patients from literature. Biallelic variants are associated with a developmental epileptic encephalopathy, characterised by severe to profound global developmental delay, usually with lack of achievement of any key milestones, absent speech, intellectual disability, and seizures. Age of onset for seizure was usually within the first year of life, and seizure onset and type were variable. No specific EEG pattern was noticed. Dystonia and movement disorders were also reported. Autistic features were present in few patients. The dominant disorder is usually characterised by global developmental delay and intellectual disability, autistic features, absent speech, but it's not associated with an epileptic phenotype.
Conclusion: We performed a comprehensive analysis of the phenotypic spectrum and epileptic features associated with *ACTL6B* variants. We carried out a differential diagnosis between *ACTL6B*-related recessive and dominant disorder and within other BAFopathies.

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WWOX developmental and epileptic encephalopathy (WWOX-DEE): understanding the epileptology and the mortality risk

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Purpose: WWOX is an autosomal recessive cause of early infantile developmental and epileptic encephalopathy (WWOX-DEE), also known as WOREE (WWOX-related epileptic encephalopathy). We analysed the epileptology and imaging features of WWOX-DEE, and investigated genotype-phenotype correlations, particularly with regard to survival.
Method: We studied thirteen patients from twelve families with WWOX-DEE. Information regarding seizure semiology, comorbidities, facial dysmorphisms and disease outcome were collected. EEG and brain MRI data were analysed. Pathogenic WWOX variants from our cohort and the literature were coded as either loss-of-function (LoF) or missense allowing individuals to be classified into one of three genetic groups: 1) LoF/LoF, 2) LoF/missense, 3) missense/missense. Differences in survival outcome were estimated using the Kaplan-Meier method.
Results: All patients experienced multiple seizure types (median onset 5 weeks, range: 1 day – 10 months); the most frequent being focal (85%), epileptic spasms (85%) and tonic seizures (69%). Ictal EEG recordings in 6/13 patients showed tonic (n=3), myoclonic (n=2), epileptic spasms (n=2), focal (n=1) and migrating (n=1) seizures. Interictal EEGs demonstrated slow background activity with multifocal discharges, predominantly over frontal or temporo-occipital regions. Brain MRIs revealed severe frontotemporal, hippocampal, and optic atrophy, thin corpus callosum, and white matter signal abnormalities. Pathogenic variants were located throughout WWOX and comprised both missense and LoF changes including five copy number variants (4 deletions; 1 duplication). Survival analyses showed that patients with two LoF variants are at higher mortality risk (p-value = 0.0024, log-rank test).
Conclusion: WWOX-DEE causes an early-infantile developmental and epileptic encephalopathy syndrome. The most common seizure types in are focal seizures and epileptic spasms. Mortality risk is associated with gene dosage; patients with two LoF WWOX pathogenic variants have significantly lower survival probability compared to those carrying at least one missense pathogenic variant.

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Prognostic value of pathogenic variants in Lafora disease: systematic review and meta-analysis of patient-level data

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Purpose: Lafora disease (LD) is a fatal form of progressive myoclonic epilepsy caused by biallelic pathogenetic variants in the *EPM2A* or *NHLRC1* genes. To date, the rate of the disease progression does not seem to be related to the type of mutated gene. We present a systematic review and meta-analysis of all the pathogenic variants reported in the literature in order to identify genotype-phenotype correlations.
Method: We collected all cases described in the literature reporting data on both disease history and pathogenic variants. The latter were classified into missense (MS) and protein-truncating (PT). Three genotype classes were then defined according to the combination of the variants: MS/MS, MS/PT and PT/PT. Time to event analysis was performed to evaluate survival and loss of autonomy.
Results: A total of 250 cases described in 70 articles were included. The mutated gene was *NHLRC1* in 57% and *EPM2A* in 43% of cases. A total of 114 pathogenic variants (67 in *EPM2A*; 47 in *NHLRC1*) were identified. The percentage of compound heterozygous was similar in *EPM2A* and *NHLRC1* cases. The *NHLRC1* genotype PT/PT was associated with shorter survival and a higher probability of loss of autonomy.
Conclusion: The study demonstrates the existence of prognostic genetic factors in LD, namely the genotype defined according to the functional impact of the pathogenic variants. Even if the reasons why *NHLRC1* genotype PT/PT is associated to a worse prognosis remain to be clarified, it could be speculated that malin has a pivotal role in LD pathogenesis.

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GABRA1-related disorders: from genetic to functional pathways

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Purpose: Variants in *GABRA1* have been associated with a broad epilepsy spectrum, ranging from genetic generalized epilepsies to developmental and epileptic encephalopathies. However, our understanding of what determines the phenotype severity and best treatment options remains inadequate. We therefore aimed to analyse the electro-clinical features and the functional effects of *GABRA1*-variants to establish genotype-phenotype correlations.
Method: Genetic and electro-clinical data of 27 individuals (22 unrelated and 2 families) harbouring 20 different *GABRA1* variants were collected and accompanied with functional analysis of 19 variants.
Results: Individuals in this cohort could be assigned into different clinical subgroups based on the functional effect of their variant and its structural position within the *GABRA1* subunit. A homogenous phenotype with mild cognitive impairment and infantile-onset epilepsy (focal seizures, fever sensitivity and EEG posterior epileptiform discharges) was described

for variants in the extra-cellular domain and the small transmembrane loops. These variants displayed loss-of-function (LoF) effects and the patients generally had a favourable outcome. A more severe phenotype was associated with variants in the pore-forming transmembrane helices. These variants displayed either gain-of-function (GoF) or LoF effects. GoF-variants were associated with severe early-onset neurodevelopmental disorders, including early infantile developmental and epileptic encephalopathy.
Conclusion: Our data expand the genetic and phenotypic spectrum of *GABRA1*-epilepsies and permit to delineate specific sub-phenotypes for LoF and GoF variants. Generally, variants in the transmembrane helices cause more severe phenotypes, in particular GoF variants. These findings establish the basis for a better understanding of the patho-mechanism and precision medicine approach in *GABRA1*-related disorders.

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Clinical spectrum and genotype-phenotype correlations of *GABRB2*-related encephalopathies

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Purpose: Pathogenic variants in *GABRB2*, encoding the β2 subunit of the $GABA_A$ receptors, have been associated with a spectrum of conditions raging from treatable epilepsy to devastating developmental and epileptic encephalopathies. Traditionally, these variants have been presumed to cause loss-of-function receptors leading to reduction of neural GABAergic activity, however, a single functional outcome for all variants is not consistent with the broad clinical observations. We therefore aimed to delineate the phenotypic spectrum and search for genotype-phenotype correlations in a cohort of patients with *GABRB2* variants.

Method: We recruited 35 patients with presumed pathogenic variants in *GABRB2*. Functional characterization of 26 missense *GABRB2* variants was performed using electrophysiology. Two functional parameters, GABA sensitivity and maximum GABA-evoked current amplitudes, were investigated.
Results: We show that pathogenic variants in *GABRB2* segregate into three distinct categories functionally: gain of function (GOF), loss of function (LOF) and gain/loss of function (GOF/LOF) receptors. Patients with GOF variants (n=18 patients) present with early infantile developmental and epileptic encephalopathies (median age-of-onset: 2.5 months), global developmental delay, severe to profound intellectually disability and severe movement disorders (choreoatheosis, dystonia, dyskinesia), as well as increased risk of early mortality. Patients with LOF variants (n=11 patients) present with generalized or combined generalized and focal epilepsy (median age-of-onset: 7.5 months), developmental delay, mild to severe intellectual disability and psychiatric and behavioral features including ADHD and autistic features. The third group of patients with GOF/LOF receptors (n=6 patients) present with later seizure onset (median age-of-onset: 24 months), global developmental delay, moderate to severe intellectual disability and severe movement disorders.
Conclusion: We demonstrate that *GABRB2* variants can lead to GOF, LOF as well as GOF/LOF a1β2g2 $GABA_A$ receptors and that the associated phenotypes are strongly linked to the functional outcome. Patients harboring GOF and GOF/LOF variants present more severe phenotypes than patients harboring LOF variants.

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De novo variants in the RNA polymerase gene POLR3B cause a developmental and epileptic encephalopathy with myoclonic seizures - detailed phenotyping of ten cases

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Purpose: *POLR3B* encodes the second largest subunit of ribosomal polymerase III, which is essential for transcription of small non-coding RNAs. Biallelic *POLR3B* are associated with an inherited hypomyelinating leukodystrophy. Recently, *de novo* heterozygous variants in *POLR3B* were reported in six individuals with ataxia, spasticity and demyelinating peripheral neuropathy. Three of these individuals had epileptic seizures.
The aim of this paper is to precisely define the epilepsy phenotype and developmental trajectory associated with *de novo* heterozygous *POLR3B* variants.
Method: We used online gene matching tools to identify nine patients with *de novo POLR3B* variants. We systematically collected genotype and phenotype data. To test a hypothesis that *POLR3B* gain-of-function may be associated with epilepsy, we did whole transcriptome analysis for *POLR3B* gene expression in a separate cohort of seven children with *SMC1A*-Developmental and Epileptic Encephalopathy.
Results: All ten patients had novel *PORL3B* variants. Patients all presented with generalised myoclonic, atonic, or tonic seizures between the ages of six months and four years. Eight patients had myoclonic seizures as part of their phenotype. Electroencephalograms demonstrated generalised spike-wave and polyspike-wave discharges but no evidence of photosensitivity. Seizures were intractable in all cases. Ketogenic diet, sodium valproate, rufinamide, prednisolone and anterior callosotomy were effective in individual patients. Additional features were: global developmental delay (9/10); ataxia/incoordination (9/10); microcephaly (3/10); and peripheral neuropathy (2/10).
POLR3B had levels of expression that were >20 times greater in patients with *SMC1A*-DEE, compared with asymptomatic age-matched controls.
Conclusion: *POLR3B* is a novel genetic Developmental and Epileptic Encephalopathy (DEE). *POLR3B*-DEE presents as a generalised epilepsy with myoclonic and/or atonic seizures in the majority of patients. An ataxic or uncoordinated gait is a common feature. Investigating whether *POLR3B* upregulation is a common epileptogenic pathway is a potential avenue for further research, and could pave the way to novel therapeutic approaches.

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Electroclinical phenotype and possible genotype-phenotype correlations in Pallister Killian syndrome: preliminary data

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Purpose: Pallister Killian syndrome (PKS), due to a mosaic tetrasomy of chromosome 12p, is characterized by intellectual disability, congenital anomalies, facial dysmorphisms, and epilepsy (40-60%). The existence of a critical region (12p13.31) where the genes responsible for the phenotype would be located has recently been postulated. The aim is to describe the electroclinical phenotype in PKS and to evaluate possible genotype-phenotype correlations; to date, literature data are few and inconsistent.
Method: Multicenter observational cohort study. Collection and analysis of clinical, electroencephalographic, neuroradiological and genetic data (with additional Nanopore sequencing when possible) in PKS patients.
Results: We collect data from 38 patients (29 prolonged EEG video monitorings, 16 standard polysomnographies). Epilepsy is seen in 26/38. For the first time, three different age-dependent electroclinical phenotypes were identified: early-onset reflex myoclonic seizures (14 pts) with subsequent good outcome; school-age onset hyperkinetic motor hypnic seizures (5 pts); early onset epileptic encephalopathy with epileptic spasms and/or tonic seizures (10 pts).
Conclusion: We detected three different, rarely co-occuring, well-defined electroclinical phenotypes. Etiologically, the most severe phenotype appears to be associated with bilateral polymicrogyria. Differently, no cortical structural anomalies were identified in the other epileptic phenotypes, thus steering towards a clear genetic nature of epilepsy in these patients. Over time, 350 genes with an altered expression have been identified in PKS patients, located both internally and externally to the critical region. We are currently evaluating possible genotype-phenotypes correlations in PKS patients by assessing epilepsy-related genes among those inside the critical region and those with an altered expression in PKS, both inside and outside the critical region (e.g. GRIN2B, NECAP1). Indeed, data obtained by Nanopore sequencing seem to confirm possible alterations outside of the critical region; similarly, recent literature has hypothesized the existence of regulatory genes located outside the critical region, which might be capable of impairing physiological DNA transcription.

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Shifting the paradigm of genetic diagnosis: an international multi-centre pilot study of rapid genome sequencing in neonatal and infantile epilepsy

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Purpose: Childhood epilepsy has highest incidence in the first year of life. A significant proportion have a genetic diagnosis with potential impacts for management including choice of anti-seizure medication. In this prospective, international multi-centre study, we aimed to demonstrate feasibility and determine the diagnostic yield and clinical utility of rapid trio genome sequencing (GS) for management and outcomes in infants with epilepsy.
Method: Gene-STEPS is the first study of the International Precision Child Health Partnership (IPCHiP), a consortium of four pediatric centres. We recruited infants (<age 12 months) with new-onset epilepsy (within 6 weeks of presentation). Clinical data were collected, and rapid trio GS was performed in clinically-accredited laboratories at each site.
Results: 100 infants had rapid GS performed with a median turnaround time of 21 days (IQR 15-23). Rapid GS made an aetiologic diagnosis in 43/100 infants (43%). Aetiologies were heterogeneous, and included diagnoses missed by standard-of-care testing. Diagnostic yield varied by age of seizure onset and electroclinical syndrome. Genetic diagnosis informed prognosis in 37/43 cases (86%), and influenced treatment in 24/43 cases (56%). Overall, 42/43 (98%) of the genetic diagnoses made by rapid GS had clinical utility for the infants and/or their families. Clinical utility was also seen for negative or secondary findings in 23%.
Conclusion: Gene-STEPS is the first study of rapid trio GS in an epilepsy cohort. We show feasibility of rapid turnaround for participants recruited from intensive care, non-intensive care inpatient, and outpatient settings across multiple healthcare systems. We demonstrate high diagnostic yield and clinical impact in infants with epilepsy. This study supports the implementation of rapid GS for infants with new-onset epilepsy. Ongoing research will examine the impact of early genetic diagnosis on developmental and epilepsy outcomes, and on the family's experience.

Genetic testing in children with pharmacoresistant genetic epilepsy in two EpiCARE centres over a two-year period

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Purpose: Drug-resistant (pharmacoresistant) epilepsies occur in approximately 30–40% of epilepsy cases. With the development of genetics, more genetic aetiologies of pharmacoresistant epilepsies are coming to attention. The aim of this retrospective observational study was to assess the genetic aetiology of pharmacoresistant epilepsy in paediatric patients in two EpiCARE centres in Slovenia and Croatia.
Method: All patients with pharmacoresistant epilepsy treated in two EpiCARE centres in 2020 and 2021 were identified from electronic health record systems using epilepsy-related ICD-10 codes. Patients who underwent genetic testing were selected to create a joined cohort and data from their medical records was collected.
Results: Of 450 patients with pharmacoresistant epilepsy, we enrolled 249 (55%) patients who underwent genetic testing. Our cohort consisted of 108 (43%) males and 141 (57%) females, with a mean age of 11.7 (SD 5.9) years. Cytogenetic analysis was performed in 30 patients (12%), Sanger analysis of specific genes, next-generation sequencing (NGS) epilepsy panels or whole exome sequencing (WES) in 92 patients (37%), and both genetic analyses in 125 patients (51%). Cytogenetic analysis detected pathogenic alterations in 28 cases (11%) and variants of unknown significance (VUS) were found in 5 cases (2%). With Sanger analysis, NGS epilepsy panels or WES we found pathogenic variants in 78 patients (31%) and VUS in 61 cases (25%). Pathogenic variants in the *SCN1A* (n=20), *TSC2* (n=7), *MECP2* (n=5), and *CDKL5* (n=3) genes were found most frequently.
Conclusion: Genetic aetiology was confirmed in 42% of cases in our cohort, but only 55% of paediatric patients with pharmacoresistant epilepsy were tested. Given the development and increasing availability of genetic testing, we recommend that genetic testing be used early in the diagnostic process in patients with pharmacoresistant epilepsy, as the aetiologic cause can be found in a high proportion of patients and the potential of precision medicine can be exploited.

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Role of genetic variation with SCN1A gene and its relation with oxidative stress in drug resistant epilepsy

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Purpose: Limited studies are available to identify the functional significance of single nucleotide polymorphisms (SNPs) in sodium channel gene (SCN1A) in drug resistant epilepsy (DRE). Higher oxidative stress is a common feature of various forms of drug resistant epilepsies, that results in increase in the serum HMGB1 levels which leads to neuroinflammation further. The current study was designed to investigate the role of SNP (rs10167228A*/T) in SCN1A gene in DRE patients to evaluate any association with increased serum HMGB1 levels.
Method: This cross-sectional study was conducted in a tertiary care hospital in Northern India. A total of 100 diagnosed Idiopathic Generalized Epilepsy patients were divided in two groups as 50 drug resistant (Group-A) and 50 drug responsive (Group-B) as per ILAE guidelines to estimate the serum HMGB1 levels and to perform the SNP study (rs10167228A*/T). The SNP analysis was performed using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. Serum HMGB1 level was estimated using CLIA based immunoassay technique.
Results: The mean age in the Group-A and Group-B were 27.30 ± 7.0 years and 22.74 ± 7.3 years respectively. Higher risk association was found with both AT and AA genotypes with odds ratio of 2.84 and 2.27 respectively (p values, 0.07and 0.08 respectively). The median serum HMGB1 levels difference was found to be highly significant ($p<0.001$) between Group-A (11.29ng/ml), and Group-B (6.02ng/ml). In ROC analysis, Cut-off value of serum HMGB1 level was 7.99ng/ml.
Conclusion: The findings support the strong association of SCN1A gene polymorphism (rs10167228A*/T) and raised oxidative stress which may be predictive for the development of DRE in such patients.

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Revisiting genetic diagnoses in adults with childhood-onset encephalitis and post-vaccination encephalopathy

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Purpose: Despite recent advances in diagnosis, the etiology of 30-60% of suspected cases of infectious encephalitis remain unclear. This number is even larger in adults who had encephalitis in childhood and were investigated 20 or more years ago. In this study, we retrospectively explored possible genetic explanations for adults with epilepsy who had a childhood diagno-

ses of infectious encephalitis and post-vaccination encephalopathy
Method: A database search was carried out to identify adult patients with a childhood diagnosis of infectious encephalitis, meningitis or post-vaccine encephalopathy at the Toronto Western Hospital's Adult Genetic Epilepsy (AGE) Clinic. Clinical history was reviewed and only patients with symptoms suggestive of those diagnoses but no microorganism growth on their CSF were included.
Results: -68 patients were identified but 44 of them were excluded due to incomplete/missing data, a confirmed or suspected case of Rasmussen's encephalitis /autoimmune encephalitis, or other causes of acquired epilepsy.
-58% (14/24) of our cohort, who were initially diagnosed with infectious encephalitis, were later found to have a genetic diagnosis of developmental and epileptic encephalopathy (DEE) in adulthood. This included pathogenic variants impacting genes such as *SCN1A, SPATA5, YWHAG, DEPDC5* and *KCNA1*. We also found a tandem repeat expansion that fell into the reported disease-causing range in *DIP2B* gene.
-57% had a diagnosis of DS, 29% had monogenic DEE, 7% had EHLMRS, and the remaining 7% were diagnosed with Jacobsen Syndrome
-67% (16/24) had medically refractory epilepsy with intellectual disability and 21% (5/24) had a formal diagnosis of autism spectrum disorder
Conclusion: Our study shows the importance of re-evaluation of childhood diagnosis. Comorbidities such as intellectual disability, autism spectrum disorder, and other complex phenotypic clues should alert the adult neurologists to reinvestigate and explore a possible genetic diagnosis.

Neuroimaging

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Pulvinar restriction diffusion: an MRI sign suggestive of status epilepticus

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Purpose: The pulvinar is the largest nucleus of the thalamus and, with its widespread connections with the cortex, it may play a crucial role in the generation or propagation of seizures. Diffusion restriction of pulvinar occurs in rare conditions such as Creutzfeldt-Jakob Disease (CJD) or occlusion of Percheron artery. However, it may represent a peri-ictal MRI abnormality of ictal or early post-ictal period in patients with status epilepticus (SE). In this study, we aimed to determine the specificity of this sign in patients with SE.

Method: Patients admitted to the Christian Doppler Klinik, Paracelsus Medical University, Salzburg, Austria between February 2019 and August 2022 and underwent a brain 3T MRI within first 48 hours after the onset of SE, were prospectively recruited. The control group comprehended patients with other neurological diseases who underwent brain 3T MRI during the same time. No patients with CJD or thalamic stroke due to occlusion of Percheron artery were imaged during the aforementioned period of time. Patients with postanoxic SE or previous history of seizures/epilepsy/SE were excluded.
Results: We included 246 patients with SE, of whom only 9 had diffusion restriction of pulvinar. In 2 patients a hippocampus was also affected and in one, an internal capsule. Arterial Spin Labeling showed concomitant hyperperfusion of a neocortex in most patients. In the control group of 1008 patients, 150 had at least one diffusion-restricted lesion. No patients in the control group had involvement of a pulvinar. Specificity of restricted diffusion of pulvinar in this cohort was 100% (95% CI 99.63% to 100.00%) with a limitation that no patients with CJD were part of the cohort.
Conclusion: Restricted diffusion of pulvinar, especially in a combination with a neocortical hyperperfusion, may represent a useful tool for diagnosing SE on MRI in patients with an equivocal electroencephalogram.

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Reduced total number of enlarged perivascular spaces in post-traumatic epilepsy patients with unilateral lesions. Results from a pilot study

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Purpose: Posttraumatic epilepsy (PTE) accounts for 20% of all structural epilepsies. MRI may play a role in risk prediction. The glymphatic system and asymmetry of enlarged perivascular spaces (ePVS) is thought to play a role in predicting the risk of PTE. We investigate ePVS to distinguish TBI-patients with PTE from TBI-patients who did not develop epilepsy by using an

automated ePVS segmentation method.
Method: The study is a retrospective observational follow up study of patients with TBI. Inclusion criteria were: >10 years post-injury, > 40 years at study session, >16 years at time of injury, moderate to severe injury. MRIs were taken between 10- and 33-years post injury. The multimodal autoidentification of perivascular spaces algorithm was applied to the cohort's T1-weighted images to segment ePVS. Lesion volume was evaluated using FSL. The total number of ePVS and an asymmetry index (AI) were calculated and divided by white matter volume (WMV).
Results: 92 controls (female=28) had TBI without epilepsy and 7 cases (female=2) had developed PTE after a mean time of 7 years (range 0-22 years). All 7 cases had MRI lesions (unilateral=4, 57%; bilateral=3, 43%) as opposed to 40 controls (total 44%; unilateral=17, 42%; bilateral=23, 58%). There was a significant difference between cases (mean $1.34e^{-4}$, 95% CI $2.89e^{-5}$, $2.38e^{-4}$) and controls (mean $3.01e^{-4}$, 95%CI, $2.07e^{-4}$, $3.95e^{-4}$) in total number of ePVS divided by WMV in patients with unilateral lesions (p=0.024). No differences in AI, mean age at injury, trauma severity and lesion volume were seen between groups.
Conclusion: In this pilot study, PTE cases with unilateral lesions had fewer ePVS compared to TBI controls who have not developed epilepsy. Further studies with larger sample sizes should be conducted to confirm findings and investigate its clinical and pathophysiological significance.

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Automated detection of hippocampal sclerosis from MRI in a multi-centre cohort of patients

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Purpose: Hippocampal sclerosis (HS) is a common cause of drug-resistant focal epilepsy that can be surgically resected. However, 20% of HS is not detected on routine visual inspection. Using a multi-centre cohort of children and adults with HS, we calculated surface-based features in the hippocampus and used these to characterise morphological abnormalities and train a machine-learning algorithm to automatically detect and lateralise HS.
Method: This study was performed on 98 patients with HS from Great Ormond Street Hospital (UK), Cleveland Clinic (USA) and Beijing Tiantan Hospital (China), 20 healthy controls and 22 disease controls (patients with FCD). The open-source software *Hippunfold* was used to segment and unfold hippocampi into surface-meshes from T1w images. Multiple surface-based features —cortical thickness, gyrification, intrinsic curvature and T1w image inten-

sity —were extracted. Features were smoothed, normalized by controls and asymmetry were computed to quantify differences between left and right hippocampi. Student's T-tests compared the mean asymmetry index of features in the hippocampi of HS patients to controls. Surface-based features were used to train a Multilayer Perceptron classifier (MLP) to differentiate HS patients from controls and lateralise the abnormality. MLP performances were tested on a withheld dataset composed of 11 controls and 22 MRI-negative HS patients.
Results: Thickness, gyrification and intrinsic curvature features were significantly different in HS compared to control hippocampi (p-value<0.05). Training a MLP using these features, the classifier accurately identified 91% of the withheld controls and detected and lateralised 19 out of 22 MRI-negative HS patients (86%).
Conclusion: Analysis of asymmetry index of surface-based features in hippocampi identified that gyrification, thickness and intrinsic curvature significantly differed in patients with HS compared to controls and patients with FCD. These features enabled highly accurate detection of HS in MRI-negative patients and could be used to aid lateralisation in the presurgical evaluation of patients with suspected HS.

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Decomposing heterogeneity in resting-state fMRI dynamics in newly-diagnosed focal epilepsy

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Purpose: The study of patients with newly-diagnosed focal epilepsy (NDfE) is crucial for an understanding of the disorder that can inform treatment pathways from diagnosis. However, there is considerable phenotypic heterogeneity in NDfE cohorts, with high interindividual variation in neurocognitive profiles, seizure semiology and in the location of epileptogenic foci in the brain. Even in more homogenous drug-resistant epilepsy patient groups, discovery of reliable diagnostic/prognostic neural signatures has proved challenging. A possible explanation may lie in dominant statistical approaches which assume neurobiological homogeneity in the case population and mask patient subtypes along the disease spectrum.
Method: Here we used latent-Dirichlet-allocation (LDA), an unsupervised machine-learning approach, to estimate relations from whole-brain temporal network features using resting-state-fMRI in 81 patients with NDfE compared to 34 healthy controls (HC) matched for age, sex and education. Input features consisted of the correlation of 22 minimally-redundant temporal characteristics between brain region pairs. Correlation coefficients were translated into absolute z-scores (disease load) by comparing each participant to multiple control group subsets.
Results: The LDA analysis identified five latent factors. We only found a significant difference between NDfE and HC in factor2 which implicated regions associated with salience/atten-

tion-ventral and limbic brain networks (pcorr=0.015). While factor2 was not related to variability in cognitive dysfunction, coding ability negatively correlated (r=-0.23, p=0.027) with factor3 (associated with salience/attention-ventral network) and logical memory was negatively correlated (r=-0.2, p=0.043) to factor1 (somatomotor network). A supervised classifier trained on all factors distinguished patients from controls with a mean accuracy test score of 73%.
Conclusion: Data-driven analysis of latent disease factors in brain network dynamics may provide a way of dealing with phenotypic heterogeneity characteristic of NDfE cohorts. In contrast to 'one-size-fits-all' statistical approaches where multiple interacting disease states are grouped together, accounting for intrinsic variability could inform patient stratification and be a step towards person-centred care.

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Brain networks and epilepsy development in patients with Alzheimer disease

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Purpose: This study aimed to investigate the association between brain networks and epilepsy development in patients with Alzheimer disease (AD).
Method: We enrolled patients newly diagnosed with AD at our hospital who underwent three-dimensional T1-weighted magnetic resonance imaging at the time of AD diagnosis. We obtained the cortical, subcortical, and thalamic nuclei structural volumes using FreeSurfer and applied graph theory to obtain the global brain network and intrinsic thalamic network based on the structural volumes using BRAPH. We compared these networks between AD patients with and without epilepsy development during follow-up.
Results: We enrolled 25 and 56 patients with AD with and without epilepsy development, respectively. Both global and intrinsic thalamic networks were significantly different between the groups. In the global brain network, local efficiency (1.340 vs. 2.401, p=0.045), mean clustering coefficient (0.314 vs. 0.491, p=0.045), average degree (27.442 vs. 41.173, p=0.045), and assortative coefficient (-0.041 vs. -0.011, p=0.045) were lower, whereas the characteristic path length (2.930 vs. 2.118, p=0.045) was higher in patients with AD with epilepsy development than in those without. In the intrinsic thalamic network, the mean clustering coefficient (0.646 vs. 0.460, p=0.048) was higher, whereas the characteristic path length (1.645 vs. 2.232, p=0.048) was lower in patients with AD with epilepsy development than in those without.
Conclusion: We demonstrated significant associations between brain networks (both global and intrinsic thalamic networks) and epilepsy development in patients with AD. The present results provide evidence that brain networks are useful biomarkers of epilepsy development in patients with AD.

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Functional connectivity of sleep disorder in patients with anti-LGI1 encephalitis

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Purpose: To explore whether sleep disorder is related to functional connectivity (FC) abnormalities in anti-LGI1 encephalitis.
Method: The FC strength of resting state fMRI was retrospectively compared in 12 cases of anti-LGI1 encephalitis with sleep disorder, 7 cases of anti-LGI1 encephalitis without sleep disorder, and 19 cases of healthy control group, with bilateral nucleus accumbens and globus pallidus as seed-point. The correlation between abnormal mean FC and sleep quality in anti-LGI1 encephalitis patients was analyzed.
Results: The FC of the shell of right nucleus accumbens, core of bilateral nucleus accumbens, lateral and medial part of the right globus pallidus, bilateral insula and operculum in the anti-LGI1 patients with sleep disorder were significantly reduced compared with the healthy control group and the anti-LGI1 encephalitis without sleep disorders ($P < 0.05$, family-wise error corrected, with threshold-free cluster enhancement 5000 permutations). After controlling the effects of age, years of education and total intracranial volume, the strength of FCs in most of these brain regions were negatively correlated with the Pittsburgh Sleep Quality Index in patients with anti-LGI1 encephalitis ($P < 0.05$).
Conclusion: The abnormal FCs associated with sleep disorder in patients with anti-LGI1 encephalitis mainly involve the bilateral nucleus accumbens, right globus pallidus, bilateral insula and operculum.

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Multimodal imaging-based diagnostic signature for MRI-negative posterior cortex epilepsy with multicenter validation

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Purpose: Posterior cortex epilepsy (PCE) primarily comprises of seizures originating from the occipital, parietal and/or the posterior edge of the temporal lobe. The lack of electroclinical relationship and subtle neuroimaging representation has rendered the diagnosis and treatment of PCE challenging in the clinical practice. In the current study, we aimed at developing novel voxel-based image postprocessing methods for better identification the neuroimaging abnormalities associated with PCE.
Method: We finally selected 165 patients with PCE as validated by postoperative pathology or presurgical evaluation from 5 epilepsy centers. Image postprocessing features were calculated over a neighborhood for each voxel in the multimodality data. The calculated maps comprised of the structural deformation, hyperintense signal and hypometabolism. Accuracy and inter-rater agreement were employed to evaluate the clinical value of the method.
Results: Five raters from 3 different centers were blinded to detect the various neuroimaging abnormalities in the calculated maps from 37 patients with MRI-negative PCE. The average accuracy of correct identification was 55.7% (range from 43.2% to 62.2%) and correct lateralization was 74.1% (range from 64.9% to 81.1%). The Cronbach's alpha was 0.766 for the correct identification and 0.683 for the correct lateralization with similar results of interclass correlation coefficient, thus indicating reliable agreement between the raters.
Conclusion: The image postprocessing method developed in this study can potentially improve the visual detection of MRI-negative PCE, a challenging disease phenotype in epilepsy. The technique can lead to increase in the number of patients with PCE who could benefit from the surgery.

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Semi-automatic interictal electric source localization based on LTM EEG: a prospective study

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Purpose: Electric source imaging (ESI) of interictal epileptiform discharges (IEDs) reached a significant yield in numerous studies. But still its implementation is labor- and cost intensive for most clinical units. Semi-automatic ESI analysis (SAEA) has been proposed as alternative and previously shown its benefit. Spike cluster have been retrieved by computer. Spike averaging and source localization is computed for each cluster. Results are reviewed by an expert neurophysiologist, to determine their relevance for the individual case. Here we examine SAEA yield in a prospective study.
Method: Between 2017 and 2022, 122 patients underwent SAEA. Inclusion criteria for the current study were: unifocal epilepsy disorder, epilepsy surgery with curative purpose, postoperative follow-up for at least 2 years. All matched inclusion criteria patients (N=40) had continuous video-EEG monitoring with 37 scalp electrodes.

Results: Mean duration of analyzed EEG was 4.3 days (+/- 3.1 days), containing a mean of 12'749 detected IEDs (+/- 22'324). For the entire group, SAEA has as a sensitivity of 74.3%, aspecificity of 80% and an accuracy of 75% for localizing the epileptogenic. Those results lead to an OR of 11.5 to become seizure-free if the source was included in the resection volume ($p< 0.05$). In patients with extratemporal lobe epilepsy our results indicated an accuracy of 68%. (OR 11.7). For MRI-negative patients (N=13) and patients requiring intracranial EEG (N=20), we found a similarly high accuracy of 84.6% (OR 19) and 75% (OR 15.9), respectively.
Conclusion: In this prospective study, SAEA of long-term video-EEG, spanning several days, we found excellent localizing information and a high yield, even in difficult patient groups (MRI negative and implanted patients). EMU presurgical evaluation should include ESI and SAEA for all patients.

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Peripheral and central nervous system biomarkers of inflammation in non-epileptic (functional) seizures: assessment with magnetic resonance spectroscopy

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Purpose: The purpose of this study was to assess the relationship between systemic inflammation, brain temperature, and brain metabolite abnormalities in functional seizures (FS).
Method: 23 FS patients and 25 psychiatric controls (PCs) underwent whole-brain Magnetic Resonance Spectroscopy and provided blood. Voxelwise choline (CHO), myo-inositol (MINO), and brain temperature were quantified with MIDAS (Maudsley et al. NMR Biomed 2006;19:492-503). Multiple linear regressions were conducted with the following serum biomarkers as covariates of interest: tumor necrosis factor receptor 1 (TNF-R1), TNF-related apoptosis-inducing ligand (TRAIL), interleukin (IL)-6, TNF-a, intercellular adhesion molecule (ICAM)-1, and monocyte chemoattractant protein (MCP)-1.
Results: In FS, higher TNF-a was related to higher temperature in the left lateral occipital cortex and fusiform gyrus, whereas in PCs, this relationship was negative. Conversely, higher MCP-1 was related to lower temperature in FS in a cluster including the precentral gyrus, postcentral gyrus, superior lateral occipital cortex, and the forceps minor and genu of the corpus callosum, and to higher temperature in PCs. Higher MCP-1 was related to higher CHO in the bilateral superior lateral occipital cortex and occipital pole (cluster 1) and the right posterior superior, middle, and inferior temporal gyrus (cluster 2) in FS, and to lower CHO in PCs. Higher TRAIL was related to higher CHO in the left middle and inferior frontal gyrus and the precentral gyrus of FS patients, and to lower CHO in PCs. Finally, higher TRAIL was also related to higher MINO in the cerebellum in FS, and to lower MINO in PCs.
Conclusion: We report two key findings. First, the relationship between serum inflammatory markers and MRS-derived markers related to neuroinflammation (brain temperature and metabolites) is different in FS compared to other psychiatric conditions. Second, this study suggests the involvement of widespread cortical and white matter regions in FS that have not

been identified previously.

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Imaging blood brain barrier dysfunction in drug resistance epilepsy: a multi-center feasibility study

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Purpose: Previous studies have linked Blood brain barrier dysfunction (BBBD) to various neurological disorders, such as seizures and epileptogenesis. To quantify and localize BBBD, we developed dynamic contrast-enhanced MRI (DCE-MRI) sequences and algorithms based on over 100 healthy controls. We showed that extensive BBBD may increase the risk for stroke, severe depression and cognitive decline. In this study, we investigate the occurrence, localization. and clinical correlates of BBBD in patients with drug resistance epilepsy (DRE).
Method: Patients (n=45) with DRE recruited for pre-surgical assessment were included. To minimize BBBD related to acute seizures, DCE-MRI was performed >48 hours after the last reported seizure. Analytic algorithms (MatLab) were used to calculate both fast and slow BBBD in 128 brain regions, using the Tofts and the Veksler models, respectively.
Results: Over 70% of patients with epilepsy had multiple brain regions with BBBD (>2SDV of controls), most often localized to fronto-temporal cortical brain regions. Those with focal seizures demonstrated significantly higher levels of BBBD compared to those with idiopathic generalized epilepsies. DCE-MRI findings of BBBD overlap with established markers of epileptogenicity.
Conclusion: These findings suggest that BBBD is a common interictal finding in DRE patients. We show that BBB imaging is feasible in patients with epilepsy and may be used as a diagnostic and pharmacodynamic biomarker. Future research is underway to examine the potential link between interictal BBBD, seizure-onset zones, seizure frequency, and epilepsy-related morbidity (e.g. cognitive performance, depression etc).

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Structural MRI biomarkers of drug-responsive temporal lobe epilepsy

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Purpose: Up to 70% of patients with temporal lobe epilepsy (TLE) are successfully treated with antiseizure medication, while 30% are drug-resistant (TLE-RS). TLE-RS is associated with mesiotemporal sclerosis that affects hippocampus, amygdala and entorhinal cortex. A third of patients with drug-responsive TLE (TLE-RSP) also present with hippocampal atrophy. Patterns of structural abnormalities in other mesiotemporal areas, neocortex, and large-scale network organization, however, remain poorly characterized. We aimed to identify lesional and network-level characteristics of TLE-RSP and compare them to TLE-RS.
Method: We obtained 3T T1-weighted MRI in 40 TLE-RSP (27 female, mean age=35±9 years) who had been seizure-free for at least 24 months with medication, 20 TLE-RS (14 female, 41±8 years), and 42 age- and sex-matched healthy controls. In surface space, we computed vertex-wise columnar volumes for mesiotemporal structures and mapped brain-wide cortical thickness according to established pipelines. To probe mesiotemporal and neocortical circuits at a subregional level, we generated high-resolution parcellations, computed inter-regional pairwise Pearson's correlations, and applied graph-theoretical covariance analysis. Patient groups were compared to controls via general linear models.
Results: Compared to controls, both TLE groups showed ipsilateral hippocampal atrophy, that was more marked and widespread in TLE-RS (d=0.71 *vs.* 0.52, all p_{FWE}<0.02). TLE-RS also displayed ipsilateral amygdala (p_{FWE}<0.02, d=0.63) and entorhinal (p<0.05) atrophy; no such changes were observed in TLE-RSP. Both TLE groups presented with bilateral fronto-temporo-parietal cortical atrophy, more marked in TLE-RS (d=0.71 *vs.* 0.59, all p_{FWE}<0.001). For both mesiotemporal and neocortical networks, the clustering coefficient and path length were higher (p_{FDR}<0.05) in TLE-RS compared to controls, indicative of network regularization. Similar findings were obtained for TLE-RSP but were not statistically significant.
Conclusion: TLE-RSP and TLE-RS present with similar severity and distribution of brain-wide cortical thinning. The lesser degree and extent of limbic pathology and network-level damage in TLE-RSP reflects milder epileptogenicity.

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Comparing ultra-high Field 7T to 3T MRI in a paediatric focal epilepsy cohort

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Purpose: Epileptogenic lesions seen in focal epilepsy can be subtle. High-field 7T MRI offers higher spatial resolution, contrast, and signal-to-noise compared to conventional 1.5/3T but its use in children is unexplored. In a cohort of 28 children with epilepsy, we compared image quality metrics (cortical thickness and gradient entropy) between paired 3T and 7T images, and calculated the rate of new reported findings in children with no findings on 3T (MRI-) and a previous PET scan.
Method: 44 children took part: 28 with drug-resistant focal epilepsy and 15 controls (8-17 years, median 13). All undertook a 3T MRI epilepsy protocol scan including 3D MPRAGE, FLAIR and T2 scans (1mm isotropic) with retrospective motion correction and a further 7T MRI session including 3D MP2RAGE (0.65mm isotropic), 3D FLAIR (0.8mm isotropic) and 2D T2 weighted sequences. All participants were unsedated. FDG-PET data were available in 20/28 patients. A multidisciplinary team and 2 neuroradiologists jointly reviewed the images with access to clinical information. On the T1-weighted images, cortical thickness was estimated with freesurfer and gradient entropy (a measure of image sharpness) was calculated in matlab.
Results: In total, only one dataset was excluded due to motion (present at both field strengths). In all patients with MRI findings at 3T (n=13), findings were replicated at 7T. In 5 3T MRI- patients with no localising features on PET, no additional findings were apparent at 7T. In the 9 3T MRI- patients with findings on PET but no findings on 3T, 5 had additional new findings. There were no additional incidental findings at 7T. Quantitatively, cortex was thinner and images sharper at 7T.
Conclusion: The proportion of MRI- children who had new findings at 7T was similar to that seen in adult studies (36%). However, in the absence of focal findings on PET, no additional abnormalities were detected at 7T.

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Does AI help to find lesions in the brain? A quantitative comparison between humans and machines

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Purpose: Focal cortical dysplasias (FCDs) are a common cause of structural epilepsy but are not visible on MRI in approximately 30% of all cases (Hauptman & Mathern, Epilepsia 2012 Epilepsia:98-104). The hope lies in Artificial Intelligence (AI) models to help in these cases. There is no gold standard for capturing human and algorithm performance or evaluating algorithms' impact on clinical decision-making. We derived quantitative measures for what it means to "find" an FCD and evaluated the performance of humans and existing algorithms and their combination.
Method: Twenty-eight human raters had to locate an FCD and its three-dimensional extent in 146 subjects. From the performance of experts, we derived acceptable thresholds for counting an FCD as "found". We additionally acquired the predictions of three algorithms and compared these to rater performance. We further defined criteria for when an algorithm could be "helpful," "unhelpful," or "distracting" and calculated the potential benefit.
Results: The average DICE score is 0.38 for experts, 0.24 for general doctors, and 0.17 for beginners. We calculated the thresholds for precision, recall, and DICE to be 0.14, 0.30, and 0.22. Using 0.22 as threshold for "finding" a lesion, one algorithm outperforms experts by 11.1% on average (81.5% vs. 70.4±7.9%). one performs similarly to general doctors (50.7% vs. 49.6±10.1%) and one slightly worse than beginner raters (30.8% vs. 32.0±2.0%).
The best performing algorithm also has a positive overall benefit for expert raters (8.9±7.4%). The other two have an overall benefit of -16.1±7.5% and -36.8±7.8%.
Conclusion: The comparison of the performance of humans and algorithms and the quantification of the impact in the form of a potential benefit shows existing algorithms to be already helpful, especially for hard-to-detect lesions, and lays the foundation for deriving guidelines for the use of algorithms in clinical practice.

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Distinct spatial patterns of gray and white matter compromise associated with the age of seizure onset in temporal lobe epilepsy

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Purpose: Temporal Lobe Epilepsy (TLE) is recognized as a network disease, involving subcortical volume loss, cortical atrophy, and white matter disruption. Previous evidence reported that cortical atrophy and white matter injury follow different spatial patterns in TLE. In this study, we seek to determine the biological processes underlying cortical gray and white matter injury with respect to the age of TLE onset.

Method: Eighty-two patients and 59 healthy controls were enrolled in this study. Cortical thickness (CT), superficial white matter (SWM), and subcortical volumes were collected. To account for the side of the seizure focus, all right-sided TLE morphometric measures were flipped to have all the structural data ipsilateral to the epileptic focus on the left side. We compared gray and white matter values between TLE and controls. We performed a series of sliding windows correlation within the group between CT and SWM, and SWM and hippocampal volume, across ages of epilepsy onset.
Results: Our findings supported the previous research, while CT presented a widespread and bilateral pattern that mainly involved the posterior brain, the SWM reported significant damages in the ipsilateral cortical structures proximal to the epileptogenic zone. The correlations reported a co-occurring atrophy in CT-SWM in the ipsilateral medial temporal lobe (MTL) when the epilepsy onset was in adulthood and a relation between the hippocampal atrophy and the whole brain SWM disruption for those patients who developed epilepsy during childhood.
Conclusion: Our results confirm distinct patterns of TLE's gray and white matter atrophy, suggesting that different biological processes likely drive these two types of injury. However, a more complex relationship may exist between cortical gray and white matter in the ipsilateral MTL when TLE onsets during adulthood. Finally, our results highlighted the critical role of hippocampal atrophy in SWM disruptions, especially in those patients who developed TLE early in life.

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A user-friendly multimodal imaging pipeline for clinical research in focal epilepsy: SWANi "Standardized Workflow for Advanced Neuro-imaging"

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Purpose: Multimodal neuroimaging approaches can contribute to identify and delineate the

epileptogenic zone (EZ) in focal epilepsies and are useful in the presurgical setting. Most of available pipelines of imaging analyses require command-line tools, sometimes difficult to implement in everyday routine. We report the methodology of SWANi "Standardized Workflow for Advanced Neuro-imaging", a processing workflow for multimodal imaging processing created under the auspicious of the NeuroImaging Commission of the Italian League against Epilepsy.
Method: By adopting a user-friendly graphical interface, SWANi is structured in two parallel workflows that use FSL and FreeSurfer tools to (a) search of the epileptogenic zone (EZ) and (b) create a multimodal scene for surgical planning. The EZ pipeline provides: voxel based morphometry analysis on volumetric T1 and FLAIR, processing of functional data [Positron Emission Tomography (FDG-PET) and Arterial Spin Labelling (ASL)], structural white-matter analyses derived from diffusion tensor imaging (DTI). The surgical planning workflow generates 3D models based on venous magnetic resonance angiography, DTI tract reconstructions and clusters derived from functional MRI (fMRI) analysis. Both pipelines provide the cortical and subcortical segmentation, cortical thickness evaluation and surface models generation
Results: Multimodal imaging data-sets of adults and paediatrics patients with surgical remediable epilepsy from 7 Italian epilepsy centers have been retrospectively analyzed with SWANi, running both pipelines (EZ and pre-surgical planning). Data were acquired using different MRI sequence/parameter combinations and field strength. Feasibility of the entire workflow has been evaluated on different workstations. Processed outputs have been explored for quality check at individual level.
Conclusion: SWANi aims to provide an easy implementation of multimodal imaging process pipelines thus fostering, together with education initiatives, the diffusion of these approaches for the management of patients with focal epilepsy, spanning from primary to tertiary epilepsy centers.

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Extent of resected mesiotemporal sclerosis predicts surgical outcome in temporal lobe epilepsy

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Purpose: Drug-resistant temporal lobe epilepsy (TLE) is often associated with mesiotemporal sclerosis involving the hippocampus (HP), entorhinal cortex (EC), and amygdala (AM). Thalamic and neocortical atrophies were also reported. While surgical resection is the current treatment of choice, ~30% of cases continue to have seizures. Advanced MRI techniques provide an excellent guide for the accurate definition of the surgical target. However, no study has assessed the interaction between MRI-derived extent of pathology, its resection, and seizure

outcome.
Method: We obtained pre- and post-operative 3D T1-weighted MRI in 55 TLE patients (29 females, mean age=37±10.4) grouped into seizure-free (TLE-SF) and not-seizure-free (TLE-NSF) and compared them to 40 age and sex-matched healthy subjects (21 females, 34.9± 12). In surface space, we computed vertex-wise volumes for HP, AM, EC, piriform cortex (PRC), thalamus and mapped neocortical thickness given established pipelines. The proportion of tissue resected with respect to the total anomaly was calculated for each structure (z-score>1.5 SD). A supervised classifier predicted post-surgical seizure outcome (5-fold cross-validation, 50 iterations).
Results: Compared to controls, patients showed bilateral atrophy (p_{FWE}<0.001) of HP (d=0.90/0.52; stronger ipsilaterally), EC (ipsi/contra Cohen's d=0.60/0.52), PRC (d=0.99/0.88), thalamus (d=0.52/0.44), and ipsilateral amygdalar atrophy (d=0.63). Bilateral neocortical thinning was observed in frontotemporal regions (d=0.57/0.55). Compared to TLE-NSF, TLE-SF had larger resection of abnormal HP (61% *vs.* 39%,) and EC (75% *vs.* 63%, $P_{FDR<}$0.001), with no differences for the rest (AM:61% *vs*. 55%; PRC:30% *vs.* 22%; temporal neocortex:15%, both). The classifier correctly predicted seizure outcome in 76% of patients (95% confidence interval). Predictive features were the extent of resected anomalies in HP and EC, plus amygdalar atrophy.
Conclusion: The main predictors for the post-surgical outcome are the amount of excised morphologically abnormal HP and EC, plus AM atrophy. A precise MRI-derived delineation of pathology bolsters individualized surgery and may assist MRI-guided thermal ablation surgeries.

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Trajectories of mesiotemporal volumes and cortical thickness in the long-term course of autoimmune limbic encephalitis

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Purpose: To quantify antibody-specific mesiotemporal and cortical atrophy rates in the long-term course of autoimmune limbic encephalitis (ALE).
Method: Individuals with antibody-positive ALE according to Graus' criteria (34 female, age at disease onset 42.5±20.4 years [mean±SD]; glutamic acid decarboxylase 65 [GAD65]: n=30, N=135 scans; leucine-rich glioma inactivated protein 1 [LGI1]: n=15, N=55 scans; contactin-associated protein 2 [Caspr2]: n=9, N=37 scans; N-methyl-D-aspartate receptor [NMDAR]: n=5, N=30 scans) treated between 2005 and 2019 at the Hospital Bonn, were enrolled. As a control group, a longitudinal, healthy cohort was included (n=42, 22 female, age at first scan 37.7±14.6 years [mean±SD], N=128 scans). Verbal and figural memory scores were retrieved from clinical records, and individuals were categorized as either impaired or unimpaired. For subcortical segmentation and cortical reconstruction of T1-weighted MRI, we applied the longitudinal framework in FreeSurfer and used linear mixed-effects models to study mesio-

temporal volumes and cortical thickness longitudinally.
Results: The amygdalar volume at disease onset was significantly higher in individuals with ALE (P≤0.048 for all antibody subgroups) compared to controls and decreased over time in all antibody subgroups, except in the GAD65 subgroup. We observed a significantly higher hippocampal atrophy rate in all antibody subgroups compared to controls (all P≤0.002), except in the GAD65 subgroup. Cortical atrophy rates exceeded normal aging in individuals with impaired verbal memory, while those who were not impaired did not differ significantly from healthy controls.
Conclusion: Our data show higher mesiotemporal volumes in the early disease stage, most likely due to oedematous swelling, followed by volume regression and atrophy/hippocampal sclerosis in the late disease stage. Our study depicts a continuous and pathophysiologically meaningful trajectory of mesiotemporal volumetry across all serogroups and suggests that ALE should be considered a whole-brain network disorder in which extratemporal involvement is an important determinant of disease severity.

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Interictal blood-brain barrier dysfunction in drug-resistant focal epilepsy

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Purpose: To investigate the integrity of the blood-brain barrier (BBB) using quantitative MRI in the interictal interval.
Method: We included 40 individuals with drug-resistant focal epilepsy (22 female, age at MRI 30±8 years [mean±SD]). All subjects underwent quantitative T1-weighted MRI imaging (qT1) after gadolinium was applied interictally (last seizure >24 hours) and natively (without gadolinium). In addition, qT1 was performed in 29 controls (12 female, age at MRI 48±18 years) without neurological diseases after gadolinium was applied and natively. Interictal scans were linearly co-registered to the native scans, and the difference native-interictal (ΔqT1) served as a surrogate imaging marker for BBB dysfunction. The mean intensity in the superior sagittal sinus was used as an internal reference to perform intensity normalization of the ΔqT1-maps. First, we used voxel-wise tests to compare the hemisphere ipsilateral to the seizure onset zone to the contralateral hemisphere and to controls in MNI152-space. Second, seizure origin zones were compared region-wise to the homotopic region of the contralateral hemisphere and to controls.
Results: Compared to the contralateral side, ipsilateral ΔqT1 was significantly higher in white matter (TFCE-corrected P<0.05) and gray matter (uncorrected P<0.05). Compared to controls, there were no significant differences related to the whole group. However, a subgroup of three individuals with hippocampal sclerosis showed significantly higher ΔqT1 bilaterally in the hippocampus and in temporal, occipital, and insular regions ipsilateral compared to controls (TFCE-corrected P<0.01). Region-wise, we observed significantly higher ΔqT1 in the

seizure onset zone compared to the homotopic region contralateral (P=0.041) and the homotopic region in controls (P=0.012).
Conclusion: Our results indicate a BBB dysfunction in drug-resistant epilepsy that persists interictally and is spatially related to the epileptogenic focus. This suggests that BBB dysfunction is less a correlate of seizures than of epilepsy itself.

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Higher diagnostic validity, half radiation dosage: Development and evaluation of a new ictal-only single-photon emission computed tomography pipeline including an arterial spin labeling control cohort

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Purpose: Ictal single-photon emission computed tomography can be used as an advanced diagnostic modality to detect ictal hyperperfusion in the presurgical evaluation of people with epilepsy. Statistical analysis of the images is limited by the availability of control images, and quantitative evaluation has yet to be conducted. Here, aimed to assess whether arterial spin labeling perfusion images of healthy control subjects can be used to enhance ictal single-photon emission computed tomography analysis and whether the acquisition of the interictal image can be omitted.
Method: Two ictal pipelines were developed: The first one uses both ictal and interictal images and compares these to healthy single-photon emission computed tomography and arterial spin labeling control subjects. The second pipeline uses only the ictal image. Both pipelines were evaluated in comparison to the current gold standard analysis. 112 individuals with epilepsy underwent ictal single-photon emission computed tomography imaging during presurgical evaluation between 2010 and 2022 and were included in the study. Fifty healthy control subjects prospectively underwent arterial spin labeling.
Results: The correspondence of the resulting hyperperfusion and the postoperative resection cavity or the presumably affected lobe was assessed using Dice score and mean Euclidean distance. Additionally, the outcome of the pipelines was automatically assigned to one of five concordance categories. Compared to the current gold standard analysis “ISAS”, both pipelines resulted in significantly higher Dice scores and lower mean distances (P<.05). The combination of both provided localizing results in 84/112 [75%] cases, compared to 56/112 [50%] generated by ISAS.

Conclusion: We propose a new and validated ictal single-photon emission computed tomography protocol, including an arterial spin labeling control cohort and acquisition of interictal single-photon emission computed tomography in non-conclusive cases only. It finds relevantly more ictal hyperperfusion and the interictal image is not needed in 72% of cases.

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Direct evidence that age-related changes in MRI-diffusion tensor imaging in the human corpus callosum represent the development of neuronal fiber myelination

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Purpose: One major developmental hallmark in the brain is the myelination of neuronal fibers. MRI visualizes age-related signal changes of the white matter, and diffusion tensor imaging (DTI) has recently enabled further quantitative analysis. Although these changes are believed to represent the process of myelination, we do not have direct evidence in humans. Myelin basic protein (MBP) is a major protein involved in myelination that can be measured by biochemical techniques. This prospective study correlated age-related changes in MRI-DTI data and the amount of MBP in the white matter of the corpus callosum obtained from patients with epilepsy who underwent corpus callosotomy.
Method: Sixteen patients (13 males and 3 females) aged 8–267 months were included. All patients underwent corpus callosotomy to treat drug-resistant epilepsy. High-resolution DTI data were obtained using 3 Tesla MRI in 14 patients, and the apparent diffusion coefficients (ADC) of the anterior corpus callosum body were individually averaged. In terms of quantification of MBP, white-matter tissues were intraoperatively collected through the conventional surgical procedure. MPB was detected with the enzyme-linked immunosorbent assay (ELISA) in 14 patients. Finally, data from the two studies were individually compared among 12 patients (9 males and 3 females). Correlations between age, ADC, and MPB were analyzed with linear or non-linear regression models.
Results: ELISA detected 9.4–22.9 pg/mL of MPB in the white matter tissues. These values were negatively correlated with those of ADC with a range of 0.65–1.3 x 10-3 mm2/s (R = -0.75). Patients' age was also correlated with values of MPB and ADC (R = 0.59 and -0.61, respectively).
Conclusion: Although this is a small pilot study, the results provide the direct evidence that age-related signal changes in the human corpus callosum identified on MRI-DTI are strongly correlated with an increase in MPB present in white matter fibers, resulting in myelination.

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Exploring dimensions of social competence in children living with epilepsy

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Purpose: Despite worldwide recognition of the affective/behavioural issues and social consequences (e.g., educational attainment) associated with epilepsy, the "social competence" (SC) of children with epilepsy remains elusive. Conceptual models of SC (e.g., Cavell TA JClinChildPsychol. 1990;9:111–122; Rantanen T et al. EpilepsyBehav. 2012;24:295-303) go beyond social adjustment (affective/behavioral functioning) to include social performance (functional independence in social behaviors) and social skills (social responsibilities: assertion/communication). We explored whether standardized parent-questionnaires used with children with epilepsy would align with theoretical models, thereby, expound our understanding of their SC.
Method: 70 children (6-12 years; male=39) with diverse seizure types and intelligence (GAI) >2nd percentile were recruited at SickKids Hospital, Toronto, Canada. Parent-questionnaires were: Behavior-Assessment-System-for-Children-Third Edition (BASC3), Scales-of-Independent-Behavior–Revised (SIBR), and Social-Skills-Improvement-System (SSIS). Factor analysis including all subscales was performed using the maximum likelihood algorithm and varimax rotation.
Results: Comorbidities included ADHD, Anxiety, and ASD. Heterogeneity was documented in GAI (range 71-119) and on parent-reported-measures; all scores significantly differed from norms ($p \leq .001$). A three-factor model explained 53% of the variance (ratio/df = 1.056434) with 23, 15, and 15%, respectively. Highest loadings were: 1-SSIS problem-behaviors, BASC3 conduct, hyperactivity, aggression, atypicality, depression, attention, and anxiety (.80, .81, .78, .71, .67, .64, .57,.50); 2-SIB-R personal-living, community-living skills, social/communication, and motor-skills (.88, .80, .79, .62); and 3-BASC3 functional-communication, leadership, and SSIS-social-skills (.72, .65, .54). Factors correspond to the Social-Adjustment, Social-Performance, and Social-Skills dimensions proposed in theoretical models. Post-hoc univariate regression analysis showed that SSIS-problem-behaviors and BASC3-anxiety, depression, and externalizing-behaviors were uniquely negatively associated with SIB-R broad (0.008, 0.005 0.04, 0.04) and SSIS-social-skills was uniquely positively associated with SIB-R broad score (0.05).
Conclusion: Conceptual models of SC were supported using standardized parent-questionnaires within a generalizable sample of children with epilepsy. Social-Adjustment and Social-Skills variables were significantly associated with overall Social-Performance. Future work will examine contributions to social cognition in paediatric epilepsy.

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Exposure-dependent effects of fetal antiseizure medications on behavior in children of mothers with epilepsy

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Purpose: Fetal antiseizure medication (ASM) exposure can produce neuropsychological abnormalities although relative risks and exposure-dependent effects are not clear across ASMs. We report here behavioral outcomes in children of women with epilepsy (WWE) taking ASMs, who are from the ongoing Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study.
Method: The MONEAD study is a prospective, observational, multi-center investigation of pregnancy outcomes enrolling WWE and healthy women during pregnancy. Children were assessed at age 4.5 years-old using the General Adaptive Composite Standard Score of the Adaptive Behavior Assessment System, Third Edition (ABAS-3), a standardized rating scale of adaptive functioning. Ratio of maximum observed ASM blood levels (ratio ABL) and ratio of defined daily dose (ratio DDD) were calculated for 3rd trimester exposures. For polytherapy, ratios were summed across ASMs. Linear regression models adjusted for multiple potentially confounding factors were conducted for both ABL and DDD exposures.
Results: 250 children of WWE were assessed at 4.5 years-old, who were primarily exposed to monotherapy (75%), and 78% of monotherapies were lamotrigine or levetiracetam. Adjusted analyses of maximum observed ratio ABL in 3rd trimester across all ASMs were significant with parameter estimate (95% CI) = -7.8 (-12.6, -3.1) (p=0.001). Similarly, adjusted analyses of maximum ratio DDD in the 3rd trimester across all ASMs were significant with parameter estimate (95% CI) = -1.94 (-3.07, -0.82) (p<.001). Secondary analyses revealed exposure-dependent effects for ratio ABL: lamotrigine (-12.0 (-23.7, - 0.3), p=.044) and levetiracetam (-18.9 (-26.8, -10.9), p<.001) and for ratio DDD: lamotrigine (-2.2 (-4.4, 0.0), p=.053) and levetiracetam (-6.6 (-9.4, -3.9), p<.001). Despite exposure-dependent effects, children of WWE did not differ from children of healthy women on the ABAS-3 (p=.766).
Conclusion: ASMs in WWE during pregnancy should be balanced to protect mother and fetus from seizures and the future child from adverse neuropsychological effects.

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Psychoses of epilepsy (POE): unravelling the phenotypic and genotypic features

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Purpose: We sought to carefully evaluate the genotypic and phenotypic features of psychosis of epilepsy (POE) in individuals recruited to a large epilepsy genetics program.
Method: A systematic search of POE cases was performed, and files reviewed to phenotype cases as well as extract relevant clinical and genetic data. Polygenic risk score analysis was undertaken using a schizophrenia common variant model.
Results: 118 people with POE were identified: 85 with interictal psychosis (72%), 26 postictal psychosis (PIP; 22%), 2 antiseizure medication-induced psychosis (2%), and 5 substance-induced psychosis (4%). Schizophrenia was the most common interictal phenotype (35/85, 41%). Focal epilepsies accounted for 85% of PIP cases, but epilepsy type was significantly more distributed in schizophrenia ($p<0.05$): 18/35 (51%) focal, 12/35 (34%) generalised, and 5/35 (14%) developmental and epileptic encephalopathy. Twenty-two POE patients (19%) had a rare genetic variant. Sixteen had a monogenic epilepsy due to PCDH19, SCN1A, DEPDC5, KCNT1, CHD2, SLC2A1, or NPRL3; four had chromosomal abnormalities; one had a variant of unknown significance. Schizophrenia was more likely to be associated with a rare variant (7/35; 20%) than PIP (1/26; 4%; $p<0.05$). Schizophrenia-related common risk variants were significantly enriched in patients with POE compared to nonepilepsy controls ($p=0.00071$); stratification of phenotypes demonstrated that only schizophrenia reached significance ($p=0.015$).
Conclusion: Interictal POE is three times more common than PIP, and more likely to be associated with both markers of diffuse epilepsy as well as rare and common genetic variants. The chronologic distinction between postictal and interictal POE is underscored by distinct epilepsy-related and genetic mechanisms.

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Healthcare providers' stigma towards people with functional seizures

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Purpose: This study aimed to explore HCPs' stigma towards people with FS. Particular focus was given to understanding HCPs' experience and knowledge of FS, discovering the attitudes held by HCPs towards working with FS as a mental health condition, and exploring HCPs' views of how their stigma manifests towards people with FS.
Method: Thirteen HCPs, who are specialised in the diagnosis and/or treatment and management of FS, were recruited through purposive and snowball sampling, and formed the final participant group. Semi-structured interviews with broad open-ended questions were utilised to obtain in-depth information from the HCPs. Their responses were analysed through a reflexive thematic process.
Results: Particularly, six main themes were identified, namely: (i) contextual factors (which indirectly influence stigma); (ii) HCPs' frustration with FS patients; (iii) HCPs' lack of knowledge; (iv) diagnostic terms; (v) stigma, and (vi) strategies to reduce stigma.
Conclusion: The findings suggest that HCPs tended to be overwhelmed with their work schedule owing to limited aid and support, and in turn were unable to provide sufficient services to their patients. Additionally, the HCPs expressed that they experienced great degrees of frustration with their FS patients, owing to their patients' inability to accept their diagnosis and overall personality. Furthermore, when the HCPs did not have an adequate understanding of FS, they were less able to shield themselves from non-factual and stigmatising beliefs about the condition. In addition, the HCPs presented with mixed reviews about their own personal stigma, with many of them also viewing their colleagues as the actual stigmatising individuals. Whilst the HCPs were able to share their perspectives on stigma towards people with FS, they also provided valuable insights in relation to strategies to reduce stigma, thus demonstrating their genuine interest in wanting the best outcomes for their patients.

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The impact of recreational cannabis on memory function in people with epilepsy

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Purpose: Cannabis is the most commonly used recreational drug in the UK with 7.6% of the population admitting regular use in national surveys, despite it remaining a class B prohibited drug in the UK. Self-reported rates of use in people with epilepsy are similar to those seen in the general population with 8.75% of people who attend our clinics reporting past or present cannabis use. This number has increased in recent years as media reports about the possible anti-seizure effects of cannabis have proliferated. Cannabis use has been associated with deficits in learning and processing speed in the general population, but little is known about the impact on cognitive function in people with epilepsy, who are already at increased risk of impairments in these domains due to the essential comorbidities of epilepsy and the side

effects of anti-seizure medications. This study examined the impact of recreational cannabis on people with epilepsy, with a particular focus on learning and processing.
Method: We compared the performance of 47 people with epilepsy who reported regular cannabis use at the time of their clinical neuropsychological assessment with 454 non-cannabis using patients on measures of processing speed, immediate memory, encoding of new information and susceptibility to distraction.
Results: People who reported regular cannabis use at the time of their clinical assessment did not differ from the non-cannabis group on measures of processing speed or immediate memory (t= -0.9, p>0.01). However they obtained significantly lower scores on the measures of sustained encoding (t=-1.7, p=0.03) and susceptibility to distraction (t=-1.9, p=0.02).
Conclusion: Recreational cannabis use in people with epilepsy amplifies deficits in new learning and enhances susceptibility to distraction in the retention of newly learnt material. These impairments are over and above those associated with the essential comorbidities of the condition and side effects of ASMs.

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Vague retellings of personal narratives in temporal lobe epilepsy

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Purpose: Aside from deficits identified in single-word level retrieval, individuals with temporal lobe epilepsy (TLE) exhibit clinical oddities, such as circumstantiality in their language production. Circumstantiality refers to the use of language which is pedantic repetitive and overly detailed. This becomes particularly evident when elicitation tasks impose minimal structure, or when impersonal narratives are retold over consecutive occasions. Personal reminiscence is highly specific and localised in time, placing unique demands on cognitive-linguistic systems. It is hypothesised that the nature of this elicitation paradigm will produce a unique psycholinguistic phenotype in those with TLE. Among controls there is a compression of output for impersonal narratives, meaning that they use fewer words over less time and are more fluent. The opposite effect is observed when personal narratives are retold.
Method: To investigate the micro- and macrolinguistic processes underpinning personal discourse production in TLE, we examined the elicited language output of in 15 surgically naïve individuals with TLE and 14 healthy controls. Participants were asked to recall and re-tell an autobiographical memory on four immediately consecutive occasions, representing an alternative unstructured elicitation. Following transcription and coding of output, a detailed multi-level discourse analysis of output volume, fluency, cohesion, and coherence was conducted.
Results: As anticipated, a distinctly different pattern emerged in TLE when compared with controls who did not compress their output volume across repetitions but instead produced greater novelty, and a more coherent and refined account over time. Individuals with TLE consistently told a less distinct story across repetitions, with disturbances in fluency, cohe-

sion, and coherence.
Conclusion: This reflects a reduced capacity to produce a coherent mental representation, in all likelihood related to the neurolinguistic demands of recalling and retelling specific personal events.

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Vagus nerve stimulation in refractory idiopathic generalised epilepsy: an Irish 'real-world' retrospective study

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Purpose: To study the efficacy, safety, tolerability, and stimulation parameters of VNS therapy in a cohort of patients with refractory Idiopathic Generalised Epilepsy (IGE).
Method: We performed a retrospective study of consecutive patients with IGE implanted with VNS therapy at Beaumont Hospital, Dublin, as part of the National Clinical Programme for Epilepsy between January 2003 and January 2022. Baseline clinical data were obtained from our epilepsy Electronic Patient Record (EPR) and paper-based medical notes. We classified 'responders' as patients with≥50% seizure reduction and 'non-responders' as those patients with <50% seizure reduction based on the information captured last clinical appointment.
Results: Twenty-three patients with refractory IGE were implanted with VNS therapy over 19 years, and 95.6% were female. Mean age was 36.3 years (range 19-55 years). Mean age for epilepsy onset was 8.6 years (range 2-14 years). The average age for the first VNS implantation was 26.5 (range 11-45, median 27). The mean duration of epilepsy at VNS insertion was 17.9 years. Median baseline monthly seizure frequency pre-implantation was 30. Median concomitant antiseizure medication was three pre- and post-implantation. Median of previously failed ASM was six (range 3-14). Seventeen patients (73.9%) had the VNS therapy switched on up to 2022. Six patients had their VNS therapy switched off due to a lack of efficacy. Among patients who continued the VNS therapy, 13 (56.5%) were considered responders. Three of thirteen became seizure-free, two had 80-99% seizure reduction, and eight had 50-79%. In the non-responder group, ten patients did not obtain a meaningful benefit from the VNS therapy. Sixteen patients reported side effects during VNS therapy, but none of the cases led to a VNS therapy discontinuation.
Conclusion: Patients with refractory IGE and high seizure frequency who failed multiple ASMs

benefit from the VNS therapy.

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Standard and investigational microburst vagus nerve stimulation elicit different fMRI brain responses

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Purpose: To investigate fMRI effects of standard versus microburst vagus nerve stimulation (VNS) parameters in a group of stimulation-naïve epilepsy subjects.
Method: 29 refractory epilepsy subjects from 8 US sites were implanted with VNS. At 2 weeks post-implantation 3 fMRI scans at 3T were conducted. Before each scan, the maximum tolerated VNS intensity was determined starting at 0.125mA with 0.125mA increments. Block-design fMRI alternated between 30s stimulation [ON] and no stimulation [OFF]: scan 1 utilized standard VNS; scan 2 optimized microburst current intensity; scan 3 optimized other microburst parameters to determine the subject's VNS settings. On-site fMRI data processing pipeline in AFNI was developed. Single-subject general linear modeling of ON-OFF blocks was performed to determine VNS-related fMRI activation per stimulation setting. Anatomical thalamic mask was used to extract mean t-value for each thalamic cluster meeting minimum thresholds (5% alpha level; 2-voxel minimum); the Peak was selected using highest mean thalamic t-value. Linear regression analyses (AFNI's 3dttest++), covarying for site and epilepsy type, were performed to create group maps for peak thalamic activation with standard and optimized microburst VNS, and to examine fMRI response differences between each (corrected $p<0.05$: voxelwise $p<0.01$, cluster threshold of 1242 mm3).
Results: Thalamic fMRI responses were obtained for scans 1 and 3 in 28 subjects (19 focal; 9 generalized). Group activation maps showed standard VNS elicited primarily thalamic activation while optimized microburst VNS showed widespread activation in addition to thalamus. Comparison of stimulation types revealed greater cerebellar, brain stem, and parietal fMRI activation in microburst VNS compared to standard VNS.
Conclusion: Standard and optimized microburst VNS both elicit thalamic activation. However, microburst stimulation also engages other brain regions, which may be uniquely involved in its mechanism of action. Relationship between fMRI activation patterns and clinical response as a potential MOA of microburst stimulation warrants further investigation.

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Probabilistic connectivity of the human cortex in patients with epilepsy

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Purpose: The human brain is one of the most mystifying networks in nature. Using intracranial EEG, effective connectivity can be probed causally by applying cortical single-pulse electrical stimulations (SPES) and recording the cortico-cortical evoked potentials (CCEPs) in connected cortices. We developed automated protocols to iteratively stimulate many cortical areas and aimed at characterizing the dynamics in effective connectivity.
Method: In epilepsy patients undergoing invasive EEG recordings for diagnostic reasons, we probed effective connectivity over 17-70 hours with randomly repeated SPES (3mA, 3 repetitions per hour) across all channels in grey matter (median: 55 [42, 100]). For each possible connection, individual CCEPs were tested for significance against surrogate time-series based on their magnitude and shape. Based on the connection probability (number of significant CCEPs relative to total SPES) in both directions, a continuous directionality index (DI) was calculated, where 0 reflects bidirectionality and 1 unidirectionality. Probability and DI were compared across all connections grouped by Euclidean distance (local ≤15mm, short-range ≤30mm, long-range: >30mm).
Results: Across 10 patients, we found 13825 cortical connections (local: 2837, short-range: 4350, long-range: 6636). The probability (P) and DI values differ as a function of connection distance (Wilcoxon signed-rank test, $p<0.001$), indicating that long-range connections (median [IQR] P: 0.41 [0.21, 0.70], DI: 1 [0.31, 1]) tend to be unidirectional and more dynamic than local connections (P: 0.99 [0.93, 1], DI: 0 [0,0.05]).
Conclusion: Using cortical stimulations longitudinally in humans with a variety of epilepsies, we unraveled new aspects of effective connectivity. We showed that most longer-range cortical connections are probabilistic and unidirectional. Characterization of cortical connectivity including its temporal dynamics a key step to better understanding the non-linear dynamics in human cortex, including the onset of seizures.

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Antiepileptic efficacy of epicranial focal cortex stimulation with a new implantable device in pharmacoresistant focal epilepsy

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Purpose: One third of patients with focal epilepsy are pharmacoresistant, and only a subgroup is eligible for epilepsy surgery. Neuromodulation is an interesting treatment option for this patient group. Here we report on the clinical efficacy of a minimal invasive approach, focal cortex stimulation (FCS) with an implantable device placed epicranially over the epileptic focus. The results are based on a pooled analysis of two prospective, first-in-man, single-arm trials.
Method: 33 patients (18 male, 15 female, age 18-75 y, mean age 34.6 y) were implanted with a 5-channel electrode placed epicranially over the individual epileptogenic focus region (temporal: 15, frontal: 9, other: 9) and a pulse generator placed in the pectoral region. Unblinded stimulation was initiated one month after implantation using combined intermittend AC stimulation at 100 Hz and DC-like stimulation for 20 min/day. A subgroup of 17 patients could additionally trigger ictal stimulation during the aware phase of a focal seizure. Intraindividual effects on seizure frequency were assessed using a mixed Poisson-model.
Results: 32/33 implanted patients underwent stimulation, and all continued treatment for a period of six months. During this period, the total seizure frequency showed a significant decrease to 52% compared to baseline in month 6 ($p<0.001$), with a 50%-responder rate after 6 months of stimulation of 53 %. Implantation-related adverse events were mild and transient and mostly consisted of local pain at the implantation site. There were no serious adverse events considered related to neurostimulation.
Conclusion: Data from these prospective trials suggest that focal cortex stimulation of the epileptic focus using an epicranially implantable device is an effective and well tolerated new treatment approach for patients with pharmacoresistant focal epilepsy. The device ("EASEE") has been CE-certified based on these data in September 2022 and provides a new available treatment option of patients with a predominant epileptic focus.

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Integrative roles of human amygdala subdivisions: insight from direct intracerebral stimulations via stereotactic EEG

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Purpose: Substantial studies of human amygdala function have revealed its importance in processing emotional experience, autonomic regulation, and sensory information; however, the neural substrates and circuitry subserving functions have not been directly mapped at the level of the subnuclei in humans. This study aims to map human amygdala functions at the level of the subnuclei.
Method: We provides a useful overview of amygdala functional characterization by using direct electrical stimulation to various amygdala regions in 48 patients with drug-resistant

epilepsy undergoing stereoelectroencephalography recordings. This stimulation extends beyond the anticipated emotional, neurovegetative, olfactory, and somatosensory responses to include visual, auditory, and vestibular sensations, which may be explained by the functional connectivity with cortical and subcortical regions due to evoked amygdala-cortical potentials.
Results: Among the physiological symptom categories for each subnucleus, the most frequently evoked neurovegetative symptoms were distributed in almost every subnucleus. Laterobasal subnuclei are mainly associated with emotional responses, somatosensory responses, and vestibular sensations. Superficial subnuclei are mainly associated with emotional responses and olfactory and visual hallucinations.
Conclusion: The novelty of this study with direct electrical stimulation of the human amygdala subnuclei reveals that the human amygdala is not only involved in basic emotions but also in more general multiple emotions. Further, the human amygdala plays an essential role in the ANS in controlling respiratory, cardiovascular, and gastrointestinal functions at the subnuclei level. The sensory symptoms elicited by amygdala stimulation highlight the direct link between the amygdala and multiple sensory processes in humans. Our findings led to the development of a functional map of the human amygdala for emotion generation, ANS regulation, and sensory information processing.

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Depression-related healthcare utilization and costs following neurostimulation for drug-resistant epilepsy (DRE)

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Purpose: Depression is a common comorbidity among patients with drug-resistant epilepsy (DRE) and is independently associated with relatively high levels of healthcare use and cost. Vagus nerve stimulation (VNS), responsive neurostimulation [RNS], and deep brain stimulation (DBS) are recommended in DRE, and the degree to which NM may impact DR care is not well understood.
Method: A US healthcare claims database was utilized to identify DRE patients who underwent VNS, RNS, DBS (2012-2019), using relevant procedure codes. Index date was the earliest date on which a procedure was identified. Patients were allocated into two cohorts (VNS, RNS/DBS) and were propensity matched. All medical claims with diagnoses of depression were deemed depression-related (DR). Use and cost of healthcare services and pharmacotherapies were assessed over 12 and 24 months. The statistical significance of differences was assessed with McNemar's tests for categorical variables and with paired t-tests and Wilcoxon signed-rank tests for continuous measures.
Results: 179 VNS patients met selection criteria and were equally matched to RNS/DBS patients. About 30% of DRE patients had evidence of depression prior to NM. VNS patients

were about one-third as likely as RNS/DBS patients to experience DR hospitalizations at 12 months (3.4% vs. 14.0%; P<0.001) and 24 months (4.5% vs. 15.6%; p<0.001). Mean (SD) DR cost for VNS patients were about one-fourth that of RNS/DBS at 12 months ($5,240 [$35,872] vs. $22,970 [$78,083]; p=0.0156) and 24 months ($5,656 [$36,104] vs. $24,228 [$79,543]; p=0.0145).
Conclusion: After matching, about 1-in-3 DRE patients have evidence of depression prior to NM. DR hospitalizations and DR healthcare costs during the 2-year period following implantation were significantly lower in VNS vs. RNS/DBS patients. Further study is needed to understand how the choice of neurostimulator impacts depression and DR care in DRE.

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Effects of a personalized tDCS protocol on magnetoencephalography source functional connectivity in patients with refractory epilepsy: preliminary findings

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Purpose: In patients with drug-resistant epilepsy (DRE), we applied transcranial direct current stimulation with several electrodes (multichannel tDCS) to decrease cortical activity with greater accuracy than with only two electrodes. Previous studies highlighted induced-changes in functional measures of global brain networks after tDCS in healthy and epileptic brains. We aimed to identify the brain regions involved in these functional changes thanks to magnetoencephalography (MEG) data acquired during a tDCS long-term protocol in patients suffering from DRE.
Method: Ten patients suffering from DRE received a 6 months therapy of tDCS with 3 cycles of stimulation repeated every two months, where each cycle corresponded to five consecutive days of 40 minutes with cathodal multichannel tDCS, personalized according to the epileptogenic zone of each patient. MEG recordings were performed before and after each stimulation cycle in order to estimate the source signals based on spatial filtering (beamforming). Functional connectivity (FC) changes were analyzed at source level to identify the induced changes in brain networks and to correlate these modifications with clinical response (seizure frequency (SF) changes).
Results: In preliminary results, 6/10 patients presented a decrease in their SF after 3 cycles of tDCS. Furthermore, we obtained a significant (p<0.05) positive correlation between SF and FC changes within the inhibited targeted brain regions.
Conclusion: Decrease in SF due to personalized multichannel tDCS was correlated with a decrease in FC within the targeted inhibited brain regions, at source level. These results suggest that tDCS-induced functional plasticity changes in targeted epileptic regions may underlie the clinical outcome differences between patients.

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Dynamics of cortical excitability and seizure resilience

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Purpose: In the formalism of Dynamical Systems theory, seizure onset can be described as a critical transition between two states: interictal and ictal. In this context, resilience to seizures is defined as the system capacity to absorb perturbation without switching state and is believed to decrease on slow timescales in epilepsy. Practically, monitoring cortical responses to minor probing perturbations may help gauge resilience.
Method: We used a mathematical model of seizures – Epileptor - to predict the cortical responses and systematically tested these predictions using both optogenetics in freely-moving mice expressing Channelrhodopsin in the right entorhinal cortex layer III (n=13), and intracranial hippocampal electrical stimulations in patients with epilepsy (n=7). Optogenetic or electrical stimulations were sequentially delivered as single-pulses (1-3ms) and pulse-trains of increasing duration (0.25-30s) until a seizure was triggered in the presence and absence of GABA-A receptor modulators. The variable cortical response to stimulation was quantified as the EEG line-length and time-to-seizure.
Results: As predicted by the model, train of stimulation induced self-sustained seizure both in non-epileptic mice and in patients with epilepsy, confirming the bi-stable nature of the limbic cortex. Benzodiazepines (BZD) increased (+71%, 95%CI [53,97]) and Pentylenetetrazole (PTZ) decreased (-19% [-5,-30]) cortical resilience (time-to-seizure). Inversely, BZD decreased (-22.5% [-18, -26]) and PTZ increased (+10% [5,17]) cortical responses to single-pulses. A machine learning approach on the EEG signal surrounding single-pulses could be used to decode momentary states of cortical excitability (f1-score: 0.88, $p<0.01$). In patients, similar decreases in cortical responses and increases in resilience were observed after administration of a BZD.
Conclusion: Theoretical predictions, that probing perturbations may help gauge cortical resilience were confirmed experimentally, using cortical stimulations in mice and humans. This work is an important step towards developing a closed-loop paradigm in epilepsy, in which seizure risk is controlled through tight cortical monitoring and timely interventions.

Nursing

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Epilepsy transition: implementing AAP/AAFP/ACP Got Transition's Six Core Elements of Health Care Transition™ 3.0

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Purpose: The purpose of this quantitative quasi-experimental quality improvement project was to determine if or to what degree the implementation of the AAP/AAFP/ACP Got Transition Six Core Elements of Health Care Transition™ 3.0 clinical practice guideline compared to current practice among epileptic patients over the age of 18.
Method: The QI project sample comprised current neurology patients over 18 years old with epilepsy requiring transition to adult care. EMR data was examined of patients with a diagnosis of epilepsy, between the ages of 18 and 30, active, and transition to adult care referral was present/absent. Patients were excluded if they were not diagnosed with epilepsy, had multiple diagnoses, and were under 18 or over 30 years old.
Results: The project included 73 (n = 25 in the comparative group and n = 48 in the implementation group) participants all between the ages of 18 to 30 years old. Data was collected from the facility's EMR. The mean age was 20.68 (SD = 1.97) for the comparative group, ranging from 18 to 27. Using chi-square, the implementation group's mean age was 20.31 (SD= 1.88), ranging from 18 to 27. The referral rate began at 24.0% (n = 6) for the comparative group and 64.6% (n = 17) for the implementation group, X^2 (1, N = 73) = 10.83, p = .001. The p-value of .001 indicates that the increase in referral rates was statistically significant. Post implementation, Ccinical significance was supported by the 40.6% increase in
Conclusion: Transition referral assessment for patient readiness is necessary to obtain earlier individualized goals and receive a seamless transition to adult care (McManus et al., 2015; White & Cooley, 2018).

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Identifying safety concerns related to antiseizure medication use in breastfeeding women with epilepsy by reviewing questions to the Norwegian drug information and pharmacovigilance centres

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Purpose: Breastfeeding has well-established health benefits for the child and the mother (Bernardo H et al. World Health O. Geneva: World Health Organization; 2013). Women with epilepsy (WWE) have lower breastfeeding rates compared to healthy women (Veiby G et al. Jama Neurol 2013;70:1367-1374). We aimed to identify the type of safety concerns among health care professionals related to antiseizure medication (ASM) during breastfeeding in WWE by reviewing questions to the Norwegian drug information and pharmacovigilance centres (RELIS).
Method: Question-answer pairs (QAPs) related to breastfeeding, epilepsy, and ASM identified by the drugs' ATC-numbers were retrieved from a searchable database containing over 55

000 QAPs using a combination of indexed and Boolean database searches and manual inspection. The QAPs were analyzed using descriptive statistics.
Results: In total, 112 QAPs were included. Most questions were from physicians, predominantly from hospitals, followed by nurses/midwives and other health care workers, in that order. Lamotrigine and levetiracetam were the ASM most frequently asked about, and antidepressants were the most prevalent co-medication. The majority of questioners called for general information about the compatibility of a specific ASM with breastfeeding. Other questions were raised due to concerns about polypharmacy or adverse effects in breastfed infants, while some questions, predominantly posed by physicians, were related to the fact that breastfeeding was not recommended in the product information. Half of the questions were posed after the women had given birth, of which half of them were asked after initiation of breastfeeding. In most cases RELIS recommended continued breastfeeding, but with specific recommendations.
Conclusion: Health care workers with presumed high competence and skills in the topic are uncertain about the prevailing safety information of ASM during breastfeeding. Future information strategies should aim to reach these professions, encourage planning medication use before birth, and support their information needs on this topic.

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Epilepsy care in a virtual world Patients lived experience of virtual care during the Covid - 19 pandemic

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Purpose: During the COVID-19 the only way to offer a service was via a virtual platform. There was limited evidence of patients experience of virtual care, this study aimed to understand the lived experience of virtual care
Method: This was a qualitative study, using a phenomenological design. The purpose was to explore everyday lived experiences of virtual care. Data was obtained by interviewing; 7 in-depth interviews were conducted before data saturation was reached. A systematic thematic analysis was undertaken and the data was then split into manageable themes.
Results: Central themes included communication. Issues such as distractions for patients in the home environment. Children, unstable internet connection for example resulted in a lapse of focus, forgetting issues and then frustration following the appointment. There was an

increased effectiveness of communication when patients had previously met teams face to face. There was a theme throughout that patients had settled for virtual because they knew that it was the only option. Comments included “face to face is more personable” “But that’s just the way it is at the moment, isn’t it?”. The strongest theme, threading through all was the importance of blended care delivery. Patients felt strongly that not all discussions should be conducted virtually, preferring face to face when severe issues arise.
Conclusion: The move to a virtual service seems one that is being continued across many services. At the onset of the pandemic this was essential. This study however shows that in the future a flexible blended approach of service delivery is preferred by patients, with the platform of review depending on home environment, clinical needs and severity of the issues being discussed. As a lead nurse and service manager this study has been important in identifying the needs of service delivery in the future.

Paediatric Epileptology

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Elucidating the fate of ‘doppelgänger’ CSWS patterns in childhood epilepsies by serial EEG and neurocognitive analysis

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Purpose: Continuous spike-and-wave during sleep(CSWS) is usually described as the characteristic EEG finding in Developmental and/or epileptic encephalopathy with spike-wave activation in sleep(D/EE-SWAS).However previous studies have demonstrated that pseudo-CSWS patterns can occur in self- limited childhood epilepsies.We aimed to identify such patterns and follow them with serial EEG and neurocognitive assessments to study their evolution.
Method: From July 2018 to July 2022,sleep EEG recording of children aged 2-12 years with “CSWS”patterns but did not satisfy complete criteria for D/EE-SWAS were included.Structural focal epilepsies with DRE for more than one year were excluded.Baseline clinical,neurocognitive and imaging data were analysed and using advanced data analysis software, spike-wave index(SWI) and stability-quotient(SQ) were assessed.Serial clinical,EEG and neurocognitive assessments were done every 6 months to identify their evolution patterns.
Results: 10 children were identified who satisfied the inclusion criteria .Based on their clinical data,EEG patterns and subsequent evolution they were grouped A)Largest group of 5 cases belonged to the pseudo-CSWS pattern in SeLEAS comprising of type 1 occipito-frontal spikes. None of them had clinical worsening and pseudo-CSWS patterns resolved within 3 years in all five cases.B)Drug induced transient “CSWS” patterns in focal childhood epilepsy syndromes:2 cases belonged to this group who had focal epilepsies,had transient exacerbation of seizures and coexistent “CSWS”patterns which completely resolved on withdrawing the causative medication(Oxcarbazepine) and no further clinical worsening seen.C)Diffusion of localized spike discharges in SeLFE syndromes mimicking “CSWS”:3 cases belonged to this group who

previously had focal spikes characteristic of SeLFE syndromes,had transient pseudo-CSWS patterns without any neurocognitive regression which subsequently resolved on followup.
Conclusion: This is the first study in literature describing the types and fate of the pseudo/"doppelgänger"CSWS patterns.Electro-clinical dissociation occur in pseudo-CSWS patterns.The differentiation of this entity from true-CSWS is important as these children do not show neurocognitive regression and therefore does not require immunomodulation.

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Risk Factors affecting Seizures after Hematopoietic Stem Cell Transplantation in pediatric patients

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Purpose: Hematopoietic stem cell transplantation (HSCT) is widely used as a treatment for patients with impaired bone marrow function. Neurological complications remain contributors to morbidity and mortality during the post-HSCT period. Since seizure is the most common clinical manifestation after HSCT, we assessed clinical profiles and risk factors of seizures to improve the prognosis after HSCT.
Method: Total of 554 children registered who received HSCT as treatment were included and who had a preexisting history of seizures before HSCT were excluded in this study. Hematopoietic stem cells were classified into allogeneic and autologous cells. All patients received pre-transplantation conditioning regimen and as a prophylaxis for graft versus host disease (GVHD), calcineurin inhibitors with or without methotrexate and other regimens were administered. The outcome of seizures included seizure freedom, development of epilepsy and death.
Results: The incidence of HSCT-associated seizures was 6.2%. Seizures were most likely to develop 100 days after HSCT and generalized seizures tended to occur nearly twice as often as focal seizures. About 70% of the seizure patients became seizure-free without requiring anti-seizure medication and 20% of patients developed epilepsy, whereas the remainder died during follow-up. Patients receiving allogeneic transplants had higher risk of developing seizures than patients with autologous transplants and using calcineurin inhibitors combined with MTX showed higher risk of developing seizures compared to patients with other regimens. Also, patients with grade 2–4 acute GVHD had a higher risk of developing seizures than those with grade 0–1 acute GVHD.
Conclusion: Our results showed that children receiving allogeneic transplants, calcineurin inhibitors with MTX for GVHD prophylaxis and having high grade of acute GVHD were risk factors for seizures, all requiring higher dose, prolonged and cumulative immunosuppressant administration. Close observation and intensive management of seizures seem to be especially necessary for these patients to improve neurological outcomes.

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A mixed methods study to develop a core outcome set for refractory childhood epilepsy treated with ketogenic diet therapy (CORE-KDT).

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Purpose: Ketogenic diet (KD) therapy can result in seizure and non-seizure related benefits for children with drug resistant epilepsy. However, clinical trials report a wide range of outcomes which makes evidence synthesis difficult and do not adequately reflect parent views on important outcomes for their child. To address this, we established the first international parent, health professional and researcher consensus to develop a core outcome set - a minimum standardised set of outcomes that should be measured and reported. (COMET registration #1116)
Method: Ethical approval was granted (London-Surrey REC19/LO/1680). A scoping review and interviews with parents identified a comprehensive list of potentially important outcomes, followed by a two-round online Delphi survey of parents and professionals to prioritise outcomes of importance for inclusion in a core outcome set. This informed a stakeholder consensus meeting and consultation process which finalised the core outcome set.
Results: In total, 97 outcomes were identified; 90 from the scoping review and seven from parent interviews. These were rationalised to 77 by the study advisory group, then rated by 49 parents and 96 health professionals in round one of the Delphi. Participants suggested 12 new outcomes for inclusion in round two, completed by 66% (30 parents and 66 professionals). Twenty-two outcomes met criteria for inclusion. Twenty-seven undecided outcomes were discussed and scored in the consensus meeting (9 parents and 13 professionals); one further outcome reached consensus for inclusion. Following the consensus meeting and ratification, 14 outcomes across five domains were included in the core outcome set.
Conclusion: A core outcome set for childhood epilepsy treated with KD therapy has been developed, incorporating the views of international parents and professionals. Implementation in research and clinical settings will standardise outcome selection and reporting, facilitate data synthesis and ultimately enhance the relevance of outcomes to parents, researchers and health professionals.

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Source-reconstructed power and functional connectivity differences between spike and spike-free periods in self-limited epilepsy with centrotemporal spikes

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Purpose: Multiple neuroimaging studies have found higher metabolic activity and functional connectivity (FC) in association to interictal epileptiform discharges (IEDs) in both awake and sleep in Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS). We implemented source-reconstruction to clinical routine and resting-state EEG (rs-EEG) to investigate differences between spike- and spike-free periods of patients with SeLECTS.
Method: Retrospectively, we analyzed 33 children with SeLECTS and 32 matched controls. We analyzed 25 epochs of 2 seconds of awake rs-EEG in five frequency bands (1-29 Hz) using source-reconstruction, power, and imaginary part of coherency (ImCoh). We compared: 1) SeLECTS without-IEDs against controls; 2) SeLECTS with-IEDs against controls; and 3) SeLECTS with-IEDs against SeLECTS without IEDs. The Desikan-Killiany atlas was employed, and one epoch before and after IEDs was discarded to control for volume conduction in the without-IEDs comparisons.
Results: In IEDs-free epochs SeLECTS presents higher ImCoh in alpha and beta1 in bilateral fronto-centro-temporo-occipital regions (p_{FWE}=0.032, d=0.62; p_{FWE}=0.039, d=0.71, respectively); lower ImCoh in theta in left parieto-occipital regions (p_{FWE}=0.011, d=0.73); and higher power from delta to beta2 in bilateral fronto-temporo-parietal regions compared to controls. In epochs with-IEDs, SeLECTS shows higher ImCoh in theta in right temporo-occipital regions (p_{FWE}=0.021, d=1.22), in alpha for left centro-parietal regions (p_{FWE}=0.007, d=1.22), in beta1 for left centro-temporo-parietal regions (p_{FWE}=0.001, d=1.34), in beta2 in left temporo-parieto-occipital regions (p_{FWE}=0.011, d=1.09); and higher power from delta to beta1 in fronto-temporo-parietal regions compared to controls. Finally, higher ImCoh in theta in bilateral temporo-occipital regions (p_{FWE}=0.016, d=1.27) and higher power from delta to alpha in bilateral fronto-temporo-parieto-occipital regions were observed in SeLECTS with-IEDs compared to SeLECTS without-IEDs.
Conclusion: In contrast to a recent sensor-level sleep and awake EEG study (Goad B et al. Clinical Neurophysiology 2022;144:123-134), source-reconstruction exposes abnormal cortical power and FC patterns and IEDs interference with normal functioning of brain networks not restricted to sleep in SeLECTS.

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Providing quality care for people with *CDKL5* deficiency disorder: an expert panel opinion on the European patient journey

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Purpose: *CDKL5* deficiency disorder (CDD) is a rare genetic disorder characterised by seizures and neurodevelopmental delays from early infancy. To address the current lack of evidence-based guidelines for standardised care of CDD in Europe, clinical experts in CDD management and patient advocacy group (PAG) representatives from across Europe convened to map the patient journey and provide expert consensus on how to ensure quality care in routine clinical practice within the European setting.
Method: Semi-structured one-to-one interviews with clinical experts in CDD management and PAG representatives were conducted by a third-party agency to avoid bias in the consensus process. The insights gained were collated into a visual representation of the Europe-specific clinical journey in CDD. Workshops followed to reach consensus and validate the journey, and to identify challenges and provide expert opinion on potential solutions or approaches for achieving Europe-wide quality care.
Results: The validated CDD patient journey has three key elements: clinical presentation/diagnosis, seizure management and multidisciplinary care. Clinical criteria for CDD diagnosis include seizure semiology and age at epilepsy onset. Genetic testing is crucial for diagnosis, especially if symptoms are atypical, allowing appropriate planning/counselling around seizure management, multidisciplinary care and outcomes. With no approved antiseizure medication for CDD in Europe, the refractory and variable seizure semiology, comorbidities, effects of polypharmacy and safety profiles of concomitant medications should be considered in seizure management. Multidisciplinary collaboration and specialist access are essential for long-term care, support and improved quality of life, with care needs changing with the patients' age and comorbidities. The expert group also highlighted much disparity in management approaches and available resources across Europe; therefore, cross-country education and knowledge-sharing are key.
Conclusion: To achieve quality care of people with CDD, European practice recommendations are required that align on realistic treatment goals, diagnostic criteria and management approaches, which can be adapted for different settings.

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Hospital-onset seizures among children aged 3 month to 12 year: a prospective cohort study

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Purpose: Hospital-onset seizures (HOS) are seizures that occur in patients admitted to the hospital for non-seizure reasons. Reported etiology and outcomes of HOS are different from out-of-hospital seizures. Not much information is available regarding HOS in children. We studied clinical profile, etiology and outcome of children with HOS at a tertiary care public hospital.
Method: For this prospective cohort study, we screened 1050 consecutive children (aged 3 month-12 year) admitted for at least 24 hours in the department of pediatrics at our hospital between 1 February, 2021 and 15 September, 2021. Children admitted within 7 days following a head injury or those admitted for seizure control during the current illness were excluded from the study. History, clinical details and investigation findings were recorded. All patients were followed daily for occurrence of seizures. Outcomes were assessed at discharge using Glasgow outcome scale (GOS).
Results: Out of the 1050 children (635 boys), 25 (2.38%) children with a median (IQR) age of 12 (4,60) months had seizures during the hospital stay. Seizures occurred at a median (IQR) interval of 21 hour (8-hour, 5 day) from admission – seizures progressed to status epilepticus in 3 (12%) children. Majority of those with seizures had a neurological condition as the admitting diagnosis. Majority of patients (68%) had a generalized tonic-clonic seizure. After neuro-infections, metabolic derangements were the second commonest etiological group for HOS (32%), with hypocalcemia being the most common. A poor outcome, defined as death/severe disability as per GOS, was seen in 8 (32%) children. Children with HOS had a 2.76 times higher risk of a poor outcome as compared to those with no seizures during the hospital stay [RR (95% CI) 2.76 (1.07-7.11), P=0.035].
Conclusion: Physicians need to be aware of the risk factors for hospital-onset seizures in children, so as to provide adequate monitoring and emergent treatment.

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Neuroimaging and neurophysiological predictors for early onset epilepsy after neonatal stroke

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Purpose: To identify predictive factors for epilepsy after neonatal stroke.

Method: 55 consecutive neonates (> 34 weeks of gestation) with neonatal stroke were included. The predominant MRI lesion was classified according to predefined criteria (Kirton A et al. Ann Neurol 2008;63:436-443). Both amplitude-integrated and whole-scalp EEG recordings from neonatal period were analyzed for background pattern, asymmetry and seizure parameters, and presence or absence of neonatal somatosensory evoked potentials (SEPs) was evaluated. Follow-up EEGs from the first year of life were classified into three categories according to the extent of epileptiform activity. Medical records were reviewed (median follow-up 80 months, range 33 - 139) as to epilepsy outcome at 1 (early onset) and 4 years of age.
Results: Of 54 surviving neonates, 10 (18.5%) were later diagnosed with epilepsy at a median age of 6.5 months (range 0 - 71). Compared to one-year-olds without epilepsy, those that developed epilepsy by age 1 (n = 6) were more likely to have infarction of proximal middle cerebral artery (MCA, $p = 0.004$), EEG asymmetry ($p = 0.036$) and uni-/bilaterally absent SEP ($p < 0.001$) and had higher total ($p = 0.041$) and maximal hourly ($p = 0.038$) seizure burden. Furthermore, they all had recurrent epileptiform activity already in their first follow-up EEG ($p < 0.001$). Except for EEG asymmetry ($p = 0.039$), there were no significant differences between children with epilepsy diagnosed between age 1 and 4 years (n = 3) and those remaining epilepsy-free at age 4. Only one child without epilepsy had marked epileptiform activity in follow-up EEGs.
Conclusion: After neonatal stroke, children with infarction of proximal MCA, EEG asymmetry, absent SEP, marked seizure burden during neonatal period, and recurrent epileptiform activity in follow-up EEGs are at risk to develop epilepsy already during the first year of life.

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PRAX-562 is a Well-Tolerated, Next Generation Anti-Seizure Small Molecule with Broad Anticonvulsant Activity in Multiple DEE Mouse Models

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Purpose: Persistent sodium current (I_{Na}), a subthreshold depolarizing current, contributes to amplification of synaptic activity and enhancement of repetitive firing. Some voltage-gated sodium channel (Na_V) gain-of-function (GoF) variants cause pathologic increases in persistent I_{Na} that contribute to the neuronal hyperexcitability observed in severe developmental and epileptic encephalopathies (DEE). We previously showed PRAX-562 inhibits persistent I_{Na} with preference over peak I_{Na} compared to standard-of-care. This profile was efficacious in two DEE mouse models with Na_V GoF mutations. Here we investigated the anticonvulsant activity of PRAX-562 in two non-Na_V DEE mouse models: *Kcnq2*$^{K556E/+}$and *Kcnc1*$^{R320H/+}$.
Method: Maximal electroshock seizure (MES) and spontaneous locomotor activity (sLMA) assays were used to assess anticonvulsant activity and tolerability of PRAX-562, respectively.

For comparison, carbamazepine and lamotrigine wer
e also assessed in MES and sLMA. Protective indices (PI) were calculated by dividing sLMA plasma TC_{50} by MES EC_{50}. PRAX-562 was evaluated on audiogenic-induced (14-kHz tone) seizures in *Scn8a*$^{N1768D/+}$ mice. Spontaneous seizure frequency was measured in *Scn2a*^{Q54} mice pre- and post-treatment with PRAX-562. The effect of PRAX-562 on latency to PTZ-induced seizures in *Kcnq2*$^{K556E/+}$and *Kcnc1*$^{R320H/+}$ mice was examined. Terminal plasma and brain PRAX-562 concentrations were measured in all experimental mice.
Results: The PI for PRAX-562 calculated as ~14x (Plasma: sLMA TC_{50} 1385ng/mL; MES EC50 102ng/mL) was greater than those calculated for carbamazepine (~3x) and lamotrigine (~6x). *Scn2a*^{Q54} and *Scn8a*$^{N1768D/+}$ mice were completely protected from spontaneous or audiogenic-induced seizures, respectively, following treatment with 10mg/kg PRAX-562. PRAX-562 (10mg/kg) was also anticonvulsant in *Kcnq2*$^{K556E/+}$and *Kcnc1*$^{R320H/+}$mice, significantly prolonging the latency to PTZ-induced seizures.
Conclusion: PRAX-562 exhibited robust anticonvulsant activity in multiple DEE (Na_V and non-Na_V) mouse models indicating broad efficacy regardless of the underlying genetic basis. Moreover, PRAX-562 markedly improved preclinical tolerability compared to standard-of-care. The profile of PRAX-562 may translate into well-tolerated efficacy in epilepsy and other indications caused by neuronal hyperexcitability.

Funding: Praxis Precision Medicines.

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Management of epilepsy with eyelid myoclonia: results of an international expert consensus panel

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Purpose: Epilepsy with eyelid myoclonia (EEM) (previously known as Jeavons syndrome) is an underrecognized generalized epilepsy syndrome. There are no randomized controlled trials for treatment of EEM, and clinical management is largely anecdotal. This project aimed to determine areas of consensus to improve the management of this syndrome given the limited available evidence.
Method: An international steering committee was convened of physicians and patients/caregivers with expertise in EEM. This committee summarized the current literature and identified

an international panel of experts, including 25 physicians and 5 patients/caregivers. The international expert panel participated in a modified Delphi process, including three rounds of surveys to determine areas of consensus for the management of EEM.
Results: There was a strong consensus for valproic acid as first-line treatment, with levetiracetam or lamotrigine as preferable alternatives for women of childbearing age. Ethosuximide and clobazam were also noted to be efficacious. There was a strong consensus to avoid sodium channel-blocking medications, except for lamotrigine, as they may worsen epilepsy. There was consensus that seizures typically persist into adulthood, with remission occurring in <50% of patients. There was less agreement about other areas of management, including dietary therapy, lens therapy, candidacy for driving, and outcome.
Conclusion: This international expert panel identified multiple areas of consensus regarding the optimal management of EEM. These areas of consensus may inform clinical practice to improve the appropriate management. In addition, multiple areas with less agreement were identified, which highlight topics for further study.

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The aetiologic and genetic landscape of infantile epileptic spasms syndrome

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Purpose: To report the aetiologies of infantile epileptic spasms syndrome (IESS) in a large cohort studied with high level genomic testing and brain imaging.
Method: Cohort of 233 infants born in Victoria, Australia during 2011-2020. Aetiology was determined by review of medical records and all clinically-performed investigations, neuroradiologist review of brain imaging, and research genomic testing. Research genomic testing was standard (>80x coverage) or high depth (400x) singleton exome sequencing (ES), followed by trio ES where singleton ES was non-diagnostic. Nineteen infants who underwent epilepsy surgery had deep ES or gene panel testing performed on brain tissue. Genetic testing was not performed in individuals with acquired aetiologies (eg perinatal stroke).
Results: Aetiology was identified in 170/233 (73%) infants, being structural in 109 (47%) (malformative 74 (32%), acquired 35 (15%)), genetic in 45 (19%) (single gene 29 (12%), chromosomal 16 (7%)), metabolic in 9 (4%), and dual diagnosis in 7 (3%). Sixty different aetiologies were identified, most commonly focal brain malformations (focal cortical dysplasia or mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy)

(31 (13%)), trisomy 21 (11 (5%)) and tuberous sclerosis (10 (4%)). The genetic basis was confirmed in 89/135 (66%) individuals with a non-acquired cause, including 32/78 (41%) individuals with brain malformations. Nine individuals (4%) had mosaic pathogenic variants, detected in peripheral tissue in 4 and brain tissue only in 5. Of the 63 infants with unknown aetiology, non-diagnostic investigations included MRI brain (63/63 (100%)), chromosomal microarray (59/63 (94%)) and genomic testing (53/63 (84%)).
Conclusion: The cause of IESS was identified in approximately three-quarters of infants; aetiologies were highly heterogeneous. Somatic variants are part of the genetic landscape and are likely underdiagnosed given the predominance of focal brain malformations, but lack of access to brain tissue limits accurate determination of their overall importance in IESS.

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Early age at seizure onset is associated with increased default-mode network connectivity in dysplasia-related focal epilepsy

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Purpose: Individuals with focal structural (lesional) epilepsy present with focal seizures at variable ages. Larger lesion size, and location within primary sensory cortex and sensorimotor networks, were associated with younger seizure-onset age in a heterogenous focal cortical dysplasia (FCD) cohort (Cohen et al. *Ann Neurol* 2022;92(3):503-511 & Wagstyl et al. *Epilepsia* 2022;63:61-74). Here we studied potential determinants of seizure-onset age in patients with bottom-of-sulcus dysplasia (BOSD), a comparatively homogenous, pathologically-distinct (FCDII) and anatomically discrete form of FCD.
Method: 85 patients (73% operated) with MRI-positive BOSD were studied. BOSDs were manually segmented on MRI. BOSD volume was calculated as a ratio of total intracranial volume. Anatomical, rostral-caudal, and functional network localisations of BOSDs were determined using brain atlas templates. Normative functional connectivity (FC) analyses were performed using each BOSD as a seed region-of-interest in resting-state fMRI data of 100 healthy, age-matched children from the ABCD study (Fair et al. 2019 NIMH Data Repositories) yielding an average FC map for each BOSD. Seizure-onset age was correlated with BOSD volumes, anatomical/network localisations, and FC maps.
Results: Median seizure-onset age was 5.4 (IQR: 2.0-8.0) years. BOSD occupied median 0.12 (IQR: 0.04-0.21)% of total intracranial volume. BOSDs were mostly located in the frontal lobe and in the frontoparietal control, dorsal attention and default-mode networks (DMN). Larger volume, location within the DMN, and increased FC to the DMN were associated with younger onset age (all $p<0.05$). No association was found between onset age and lobar location, proximity to sensorimotor cortex, or rostral-caudal location.
Conclusion: In addition to volume, anatomical location of BOSD within and increased FC to

the DMN correlated with younger seizure-onset age. In contrast to previous findings, location within sensorimotor cortex and networks did not correlate with younger onset in our BOSD cohort. The DMN "comes online" in early childhood and may influence seizure-onset age.

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Efficacy of soticlestat treatment by seizure type in patients with Dravet syndrome or Lennox–Gastaut syndrome in a phase 2, randomized, placebo-controlled study (ELEKTRA)

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Purpose: Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) involve developmental delay and frequent treatment refractory epileptic activity. The published ELEKTRA study investigated the efficacy and safety of soticlestat, a cholesterol 24-hydroxylase inhibitor, in children with DS or LGS. This *post hoc* analysis of ELEKTRA investigated the efficacy of soticlestat by seizure type.
Method: ELEKTRA (NCT03650452) was a phase 2, randomized, double-blind, placebo-controlled study of adjunctive soticlestat (≤300 mg twice daily, weight-adjusted) in children aged 2–17 years with DS (≥3 convulsive seizures/28 days) or LGS (≥4 drop seizures/28 days). The primary endpoint was change in convulsive (DS) and drop (LGS) seizure frequencies. *Post hoc* efficacy analyses determined percentage change from baseline in seizure frequency by type. Patients' caregivers recorded seizure number and type throughout the baseline and full (20-week) treatment periods, including generalized tonic–clonic, focal to bilateral tonic–clonic, focal with motor signs, and atonic seizures.
Results: Of 141 enrolled patients, 126 (89%) completed ELEKTRA. The modified intent-to-treat population received ≥1 study drug doses and had ≥1 efficacy assessments (DS, n=51; LGS, n=88). Median seizure frequency changes from baseline in patients with DS receiving soticlestat (placebo): generalized tonic–clonic seizures, −27.2% [n=14] (19.5% [n=21]); focal to bilateral tonic–clonic seizures, −73.9% [n=9] (8.4% [n=4]). Median seizure frequency changes from baseline in patients with LGS receiving soticlestat (placebo): generalized tonic–clonic seizures, −33.4% [n=17] (−20.0% [n=11]); focal to bilateral tonic–clonic seizures, −41.3% [n=6] (none); focal seizures with motor signs, −64.3% [n=10] (−21.1% [n=7]); atonic seizures, −33.9% [n=16] (−17.9% [n=13]).
Conclusion: Reduced median frequency of specific seizure types was observed in patients receiving adjunctive soticlestat, warranting further investigation into its use for treating these seizure types in other epilepsies (two phase 3 studies are ongoing for DS and LGS).

Study funded by Takeda Pharmaceutical Company Limited.

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Comparative efficacy and safety of stiripentol, cannabidiol and fenfluramine as first-line add-on therapies for the treatment of seizures in Dravet syndrome (DS): a network meta-analysis study

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Purpose: Stiripentol has been licensed internationally and used widely since 2007 as an add-on therapy to manage frequent seizures in DS. More recently, cannabidiol and fenfluramine have been licensed; however, there are no comparative trials of these therapies. We assessed their comparative efficacy and safety as first-line add-on therapies to standard-of-care anti-seizure medicines in DS.
Method: Bibliographic databases and regulatory documentation were systematically searched for randomised controlled trials (RCT) of licensed add-on therapies for DS. Outcomes of interest were the proportions of patients achieving reductions from baseline in monthly convulsive seizure frequency (MCSF) of ≥50% (clinically meaningful), ≥75% (profound) and 100% (seizure-free), and the proportions experiencing serious adverse events (SAEs) and discontinuations due to AEs. Comparative efficacy and safety were assessed using frequentist network meta-analyses (NMAs).
Results: We identified relevant data from 2 placebo-controlled RCTs for each intervention. Higher proportions of patients achieved ≥50%, ≥75% and 100% reductions in MCSF with stiripentol 50mg/kg/day Vs. fenfluramine 0.7mg/kg/day: absolute risk difference [RD] 1% (95% credible interval: -20% to 22%; p=0.93), 6% (-15% to 27%; p=0.59) and 26% (8% to 44%; p<0.01), respectively. Stiripentol was also superior (p<0.05) to all licensed cannabidiol dose regimens (10 and 20mg/kg/day; +/-clobazam) for these efficacy outcomes.
Lower proportions of stiripentol-treated patients experienced SAEs and discontinuations due to AEs compared to fenfluramine: absolute RD -8% (-29% to 14%; p=0.48) and -18% (-36% to -1%; p=0.04), respectively. Similarly, lower proportions of stiripentol-treated patients experienced these safety outcomes compared to all cannabidiol regimens, with discontinuations due to AEs being significantly (p<0.05) lower compared to cannabidiol 20mg/kg/day regimens (+/- clobazam).
Conclusion: NMAs using RCT data indicate stiripentol, as a first-line add-on therapy in DS, is at least as effective as fenfluramine and more effective than cannabidiol in reducing convulsive seizures, with no greater risks of SAEs or discontinuations due to AEs.

Disclosure: Funded by Biocodex.

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Clinical profile and short term outcome of neonatal and early onset epilepsies in South Indian children – experience from a prospective cohort

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Purpose: We evaluated the clinical characteristics and short term outcome of a prospective cohort of neonatal and early infantile onset epilepsies attending a tertiary care pediatric epilepsy centre in South India.
Method: Consecutive infants less than 3months of age who presented with seizures, were enrolled into the study between June 2020 to September 2021. Infants with acute symptomatic seizures were excluded. All infants underwent EEG imaging and basic metabolic screen. Genetic testing was done when deemed relevant by the treating physician. All infants were followed up for a minimum period of 6 months. Developmental and epilepsy outcomes were assessed at last follow up.
Results: Among 86 consecutive infants, 58 with acute symptomatic seizures were excluded. Male : female ratio was 8: 20. Median age at seizure onset was 30 days (Range- 2 to 83 days). 15 had seizure onset in the neonatal period (<28 days). 7 infants had lesional epilepsies -FCD with tuberous sclerosis(2), complex cerebral malformations(3), cystic encephalomalacia(2). 18/28 underwent genetic analysis. Damaging variations were found in 7 children. Variations detected were- KCNT1(1), KCNQ2(1), SCN1A (1), CDKL5(1), UGP2(1), MOSC2 (1), and 1p36 deletion. 8/18 were variants of uncertain significance (KCNT1, KCNQ2, TUBA3D, PACS2, BCKDHB, RKT1, ATP1A3, and chromosome 20 microdeletion). 3 infants showed no variation. Follow up period ranged from 6 to 19 months. Mean age at last follow up was 11.4 months. 2 children expired during follow up. At the time of last follow up, 5 children had attained seizure remission, 17 were on more than 3 anti-seizure medication (Range- 1 to 6). 18 children had significant neurodevelopmental delay.
Conclusion: This study reports the profile of early onset epilepsies in South Indian children. Large multicentric collaborative efforts are needed to further characterize the distribution of complex early onset epilepsies across regions and populations.

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Seizures in neonates: electro clinical findings and prognostic factors

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Purpose: Purpose: To analyze the electroclinical characteristics of newborns with seizures and to identify predictive factors for epilepsy and developmental delay.
Method: Methods: We included 81 newborns with seizures admitted to the NICU between 2018-2021. Clinical, EEG and video electroencephalographic findings were collected. A semi-structured survey was carried out to evaluate neurodevelopment.
Results: From 10,495 live births, 81 presented a neonatal seizure, prevalence of 0.77%, The most reported etiology was genetic 28% followed by hypoxia ischemia 26%. Regarding seizure

semiology, newborns with genetic etiologies presented: tonic seizures 39%, clonic seizures 30% and sequential 13%. Patients with hypoxia ischemia presented clonic seizures more frequently (62%), 50% with metabolic etiology had myoclonic seizures and 33% sequential seizures and newborns with structural etiology, 47% tonic seizures.Patients with sequential seizures (n=5), 80% were of genetic etiology (n=4) (p=0.008), followed by metabolic causes, highlighting a distinctive pattern. Of our cohort, 11 (8.6%) patients died within the second month of life mostly due to infections. In the survival group (77p), the 57% (40p.) developed epilepsy and 45.7% (32p.) developmental delay. 62.5%(25p.) who developed epilepsy had developmental delay (p< 0.05). 100% (4p.) with infections and 80%(16p.) with genetic causes developed epilepsy, (p=0.015), regardless of seizure semiology and EEG findings. Regarding the EEG, 34.6%(28p) had a burst suppression pattern; 17.8%(5p) died, 65% (15p) developed epilepsy and 47% (11p) presented developmental delay. 3.7% (3p) with a normal EEG background died and 41,6% (10p) developed epilepsy and developmental delay.
Conclusion: This is the first prospective study in Argentina of neonatal seizures and electroclinical features. Seizure semiology observed was similar with what is reported regarding to etiology. Newborns who developed epilepsy presented developmental delay more frequently. Burst suppression wasn`t associated with an increased risk in mortality or epilepsy. Genetic, infections and hypoxia ischemia etiologies were mostly associated with developmental delay and epilepsy.

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HMGB1 and TLR4 as biomarkers for refractoriness of SE in small children

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Purpose: High mobility group box protein 1 (HMGB1), a protein released by glia and neurons during inflammation, and HMGB1/TLR4 axis play a role in initiation of neuroinflammation. The purpose of this study is to investigate the association of serum high-mobility group box-1 (HMGB1) and toll-like receptor 4 (TLR4) in status epilepticus (SE) in small children.
Method: Fifty five children aged 1month -4 years, diagnosed with SE and forty eight healthy controls were enrolled in this case-control study in 2021-2022, in Hospital of Mother and Child Health Care, Moldova. We collected serum samples for assessment of HMGB1 and TLR4 by enzyme-linked immunosorbent assay (ELISA).
Results: Serum HMGB1 was elevated in 38 patients compared to 2 patients in control group (p<0.001) and the level of TLR4 was increased in 22 patients with SE vs 1patient from control (p<0,001) which demonstrates the role of inflammation in pathogenesis of SE. The highest values of HMGB1(>2000 pg/ml) and TLR4 (>10 ng/ml) were found in nonconvulsive SE, in patients admitted in ICU, so can be concluded the role of these markers in prognosis of desease. HMGB1 and TLR4 expressions were higher in seizures lasting more than 10 min compared to those with a shorter duration (p<0,001) and in refractory SE comparing with established SE (p<0,05).

Conclusion: The increased levels of HMGB1 and TLR4 have demonstrated the role of inflammation for the refractoriness of SE in small children and we can assume that the addition of drugs with anti inflammatory properties would be beneficial in sever cases of SE.

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PAGE - Paediatric autoimmune and genetic testing in epilepsy: a novel paradigm in the rapid diagnosis of treatment-resistant epilepsy

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Purpose: Children with treatment-resistant epilepsy (TRE) have a significant disease burden and their care typically follows nonuniform diagnostic protocols, causing lengthy diagnostic odysseys. Diagnosis can inform management, as seen in at least a quarter of genetic, and almost all autoimmune diagnoses. However genetic and autoimmune testing is often offered at later stages of the pathway.
Method: PAGE is a prospective cohort study that investigates the utility of combined genetic and autoimmune testing in a cohort of children with newly diagnosed TRE. Participants are offered comprehensive genetic testing, genetic counselling, and panel-based neural antibody testing incorporating tissue indirect immunofluoresence (TIIF) at their first visit. They also complete baseline and follow-up treatment and satisfaction questionnaires.
Results: We have enrolled 35 participants (median: 4.5 years), 54% (n=19) were female. Developmental epileptic encephalopathy was diagnosed in 20% (7/35) of patients. Diagnostic yield was 33% (10/30) for genetic testing and 3% (1/33) for autoimmune testing. Those with a genetic diagnosis had a lower age of onset of seizures (1.7 vs 4.4 years), with the most common diagnosis being SCN1A-related disorder. Changes in seizure management, clinical care and prognosis based on genetic results occurred in 90%. In those with positive autoimmune results (n=3), two were weakly positive for GAD65, which is clinically insignificant. All individuals with positive neuronal antibody testing had an alternative genetic diagnosis. In follow-up surveys participants reported 90% satisfaction with testing offered, and 86% agreed that genetic counselling improved their disease understanding.
Conclusion: This study provides novel insights into the benefits of timely genetic and autoimmune testing in the TRE diagnostic pathway. While we found autoimmune-associated epilepsy to be rare in children, clinical impact of timely comprehensive and combined testing, as well as increased patient and family satisfaction from informed decision-making warrants consideration for improved diagnostic guidelines for paediatric TRE.

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Multi-day seizure cycles are similar in paediatric and adult epilepsy

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Purpose: Multi-day seizure cycles are defined by the tendency for seizures to recur at periodic intervals over days, months or even years. These cycles are documented extensively in adults, but emerging evidence suggests that similar rhythms exist in paediatric epilepsies. These multi-day cycles underpin models of seizure likelihood used to forecast future periods of seizure risk, however, this approach is yet to be explored in a paediatric cohort. Therefore, the current study used established methods of seizure forecasting to identify, and compare, multi-day seizure cycles between children and adults with epilepsy.
Method: 220 participants (48 paediatric) with confirmed epilepsy were recruited (St Vincent's Hospital HREC 165.19). Participants reported seizure times in a mobile epilepsy management app for a minimum of 28 days. Circadian (0.5 - 2.5 days) and multi-day (3 - 28 days) seizure cycles were quantified using the synchronisation index (SI), measuring the synchronisation of seizure times to an underlying cycle. Cycles were grouped using k-means clustering and the distributions of cycle strength within each group were compared between paediatric and adult participants (Wilcoxon rank-sum and Kolmogrov-Smirnov tests).
Results: Participants reported 37,663 seizures (M = 69, SD = 146) between September 2018 and May 2022. Significant multi-day cycles were found for paediatric and adult participants. Clustering identified 3 multi-day cycle periods, centred at 6, 14 and 23 days, in addition to circadian cycles. There were no significant differences ($p > 0.05$) in the strength of seizure cycles between paediatric and adult participants, or between males and females, for any of the cycle clusters.
Conclusion: The current study identified similar multi-day seizure cycles in both paediatric and adult populations. These findings suggest that seizure risk forecasting may be possible in children using methods already established in adults, which could be valuable in managing and treating epilepsy in children.

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Genetic etiology in pediatric epilepsies manifesting status epilepticus

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Purpose: Status Epileticus (SE) is a life threatening condition requiring rapid recognition and treatment. SE is rather frequent in children and has very heterogeneous etiologies. We present a retrospective-observational study on etiologies of pediatric epilepsies manifesting convulsive status epilepticus (SE), with emphasis on genetic etiology.
Method: The Italian Pediatric Status Epilepticus group (IPSE), which includes 11 centres variously distributed throughout the country, collected clinical and genetic data from 1063 children with SE over the past 10 years. We present data of 776 selected patients who had epilepsy, either preceding or following the SE.
Results: Median age of SE onset was 3 years (IQR 1-8). In 223 patients the aetiology was structural either acquired (21.5%) or genetic (25%). In 453 patients (58.3%) the aetiology was genetic which was known in 199 (44%) carrying either single gene pathogenic variants (158) or chromosomal abnormalities (40) and in 254 patients (56%) the genetic origin was presumed. Remaining patients had the following aetiologies: post-infectious (9), neurometabolic (18) and neuroimmune (20) while in 6.8% (53) the cause remained unknown. Refractory SE was observed in 52.3% of the patients with known genetic aetiology and in 34.3% of those with presumed genetic causes. Monogenic epilepsies involved 63 genes including sodium, potassium, calcium and GABAA channel subunits, genes involved in synapses function and mTOR pathway and others whose function is not understood.
Conclusion: Etiology of epilepsies manifesting SE has an underlying genetic origin in over 50% of patients. Refractoriness rate is significantly higher in patients with known than presumed genetic etiology. Single gene mutations are the most frequent findings warranting the inclusion of genetic analyses in the diagnostic workup of patients with SE.

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Epilepsy apps: embracing technology to improve patient experience

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Purpose: Identifying epilepsy tracking phone applications and their use by patients and clinicians. Determining if apps can give patients more input into their care by harnessing valuable

data on seizure type(s), frequency, medication compliance, emergency medication use etc. which can be shared directly with professionals.

Method:

1. Survey of HCPs (Consultants, Junior Doctors and Clinical Nurse Specialists)
2. Survey of parents/patients
3. Identifying and comparing apps which met inclusion criteria:
    1. Primary Criteria:
        1. Free
        2. Available on both iPhone and Android
    2. Secondary Criteria. (At least 3):
        1. Seizure diary
        2. Video capture/sharing
        3. Medication diary
        4. Side Effects
        5. Seizure Triggers
        6. Use of emergency medications
4. Meetings with app developers (Young Epilepsy and Seizure Tracker) to consider integration.

Results: Apps were rarely used by clinicians (50% not using) or patients (100%), and knowledge of their functionality was limited. Both groups felt video recording (88%, 100%) and stopwatch timers (67%, 88%) were key utilities. Clinicians prioritised ease of sharing (59%,13%) while parents wanted appointment reminders (59%, 63%)
4 apps met the criteria above; Seer, Nile, Seizure Tracker and Epilepsy Journal. All had seizure and medication diaries with trigger recording . Only Seizure Tracker allowed video recording via the app, combined with a stopwatch and emergency medication/VNS timer. All except Nile created downloadable and shareable PDF reports.
Seizure Tracker seemed to best fit the needs of our population, and was the one most frequently recommended already by clinicians (26%).

Conclusion: There is both appetite and opportunity to harness the data recorded in epilepsy tracker apps. If patients are able to upload and share data directly, it allows clinicians to track changes more accurately and in a timely manner.

When information is available in advance of clinical review, more time can be spent focussing on the patient's concerns rather than information gathering, which leads to improved patient experience.

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Long-term treatment with ganaxolone for seizures associated with CDKL5 deficiency disorder: 2-year open-label extension follow-up

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Purpose: Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a developmental and epileptic encephalopathy characterized by global developmental impairment and early-onset, refractory seizures. In a recent double-blind placebo-controlled study, ganaxolone significantly reduced major motor seizure frequency (MMSF) in patients with CDD. Here we report on safety and clinical outcomes data through 2-years open-label extension (OLE) treatment.
Method: Patients with CDD (aged 2-19 years) who completed the double-blind phase were eligible to receive ganaxolone in the OLE. Assessments included percent changes in MMSF from pre-randomization baseline to 3-month intervals in the OLE, safety, and tolerability. All patients in this analysis had entered the OLE at least 2-years prior to data cut off (June 30, 2022).
Results: Eighty-eight (of the 101 randomized) patients (87.1%; median age of 5; 79.5% were female) continued into the OLE. The median baseline 28-day MMSF was 50.6. Within 2 years in the OLE, 37 patients discontinued for the following reasons: lack of efficacy (n=13), withdrawal by caregiver (n=11), adverse event (n=10), physician decision (n=2), and death (n=1). Using all available data at 2 years in the OLE (Months 22-24), patients (n=50) experienced a median 48.2% reduction in MMSF. When imputing missing data using last observation carried forward, patients (n=87) experienced a median 27.4% reduction in MMSF at 2 years. The most commonly reported treatment-emergent adverse events in the OLE were seizure (23.9%), vomiting (22.7%), somnolence (21.6%), and pyrexia (17.0%). There was one death reported due to sepsis, but it was deemed unrelated to study treatment.
Conclusion: Sustained reductions in MMSF at 2 years provide supportive evidence for the maintenance of effect of ganaxolone in seizures associated with CDD. Ganaxolone was generally well-tolerated in the OLE with safety findings consistent with the double-blind phase.

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Prognostic factors for neurocognitive outcome in children with periventricular nodular heterotopias

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Purpose: Periventricular nodular heterotopias (PNH) result from a failure of neuronal migration during brain development. They can occur in isolation or associated with other brain malformations, and are typically related to focal epilepsy. The main objective of this study is to identify prognostic factors for neurocognitive outcome in individuals with PNH.
Method: Descriptive and analytical study of a cohort of 46 children diagnosed with PNH. We reviewed their clinical, genetic and neuroimaging features and performed neuropsychological assessments including Wechsler scales, Vineland adaptative Scale-III and behavioural scales.
Results: Twenty-four individuals (52%) had isolated PNH, whereas 22 were associated with other brain malformations (mainly cortical development malformation, midline abnormalities or posterior fossa malformations). Twenty-two subjects (48%) had epilepsy, 14 within the group with associated brain malformations and 8 within the isolated PNH group, (58 and 33% of these groups, respectively). Epilepsy onset occurred in the first 2 years of life in 77% of patients, in childhood in 9% and in adolescence in 13%. The median IQ in the whole cohort was 83, within the lower-middle values, ranging from 27 to 111. The median IQ in individuals with epilepsy was 21,5 points lower than in those without epilepsy (IQ 85 vs. 63,5). In the same way, the median IQ was lower in subjects with brain malformations (IQ 67) than in the isolated PNH group (IQ 83). Among individuals with epilepsy, those with an early onset showed the lowest IQ (60 vs 83 in those with a later onset). Twenty per cent of individuals had some risk indicator for autism spectrum disorder, with higher percentages among individuals with epilepsy or complex brain malformations.
Conclusion: PNH may be the cause of paediatric-onset epilepsy and neurodevelopmental disorders. The coexistence of other brain malformations as well as early onset of epilepsy appear to be risk factors for a worse neurocognitive prognosis.

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Rolandic epilepsy: phenotypes and comorbidity matrix from a pan-European cohort of 200 patients

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Purpose: Rolandic epilepsy (or SELECTS in the new ILAE terminology) is a common paediatric epilepsy syndrome. Comorbid neurodevelopmental disorders are recognised but their combined prevalence or interrelationships have not been appreciated.
Method: Patients were recruited by trained clinicians through paediatric specialist centres for a genetic study, ascertained on an EEG report showing centrotemporal spikes. We used international definitions and validated data collection instruments for the epilepsy syndrome and the comorbid disorders of interest. We calculated summary statistics and odds ratios of association using logistic regression.
Results: Patients were recruited by trained clinicians through paediatric specialist centres for a genetic study, ascertained on an EEG report showing centrotemporal spikes. The cohort is 58% male with a median age of seizure onset 7.7 years and age at survey of 11.6 years. At recruitment, the median number of seizures was 5 (range 1-10+). All seizures were sleep-related; involving the face (61%), guttural noises (63%), drooling (74%) aphasia (84%), with preserved awareness (46%); 39% had experienced definite generalised tonic-clonic seizures; 69% had ever been treated. Comorbid disorders included ICD-10 defined reading or learning difficulty (45%); ICD-10 speech sound disorder (41%); borderline or abnormal ADHD symptom score (37%); probable developmental coordination disorder using DCDQ07 (31%); ICHD-2 migraine features (20%). Sixty-nine percent had at least one neurodevelopmental disorder (NDD) ie speech/reading/learning/DCD/ADHD. NDDs were significantly associated with each other: Speech/Reading Odds Ratio 7.82, Speech/DCD OR 4.92, Speech/ADHD OR 4.54, Reading/DCD OR 9.80, Reading/ADHD OR 8.87, DCD/ADHD OR 4.89.
Conclusion: The high symptom prevalence and strong associations across motor, speech, attention and reading categories support the concept of Rolandic epilepsy as a neurodevelopmental disorder with self-limiting, focal seizure semiology. The findings inform future attempts at classification, analysis strategy for genomewide association study and invite genetic correlation with neurodevelopmental traits in population cohorts.

1026

Longitudinal volumetry of subcortical gray matter in Rasmussen's encephalitis

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Purpose: To investigate subcortical gray matter volumes and asymmetries in Rasmussen's encephalitis (RE) longitudinally, emphasizing clinically relevant subgroups.
Method: We included 59 individuals with RE (37 female, median age at onset 8 years, range [1, 51]), with a total of 384 T1-weighted MRI scans available (1 to 20 per case). Subcortical segmentations were performed using FreeSurfer. We used subcortical volumes (caudate nucleus, amygdala, hippocampus, and putamen) relative to total intracranial volume (or ipsi-/contralateral-ratio) as dependent variables in linear mixed-effects models. As fixed effects,

we included age at disease onset, sex, affected hemisphere, and the interaction disease duration*hemisphere (or disease duration*group). All cases were classified as type 1 (n=27, age at onset ≤6 years) or type 2 (n=32, age at onset >6 years) according to Bien et al. (Brain 2002;125(8):1751-1759), and into groups with (n=26) or without (n=33) contralateral EEG abnormalities.
Results: In type 1, we found significant atrophy of all four structures ipsilateral (all P<0.05) and the contralateral putamen (P=0.048). In type 2, we found significant atrophy of the ipsilateral caudate nucleus and putamen (both P<0.05). Regarding the ipsi-/contralateral-ratio, we found significantly greater atrophy of the ipsilateral hippocampus and amygdala in type 1 than in type 2 (both P<0.001). In cases with contralateral EEG abnormalities, we found significant atrophy of the ipsilateral caudate nucleus, hippocampus, and putamen (all P<0.025). In cases without contralateral EEG abnormalities, we found significant atrophy of the ipsilateral caudate nucleus and putamen (both P<0.01). Regarding the ipsi-/contralateral-ratio, cases with contralateral EEG abnormalities showed significantly greater atrophy of the ipsilateral caudate nucleus, amygdala, and hippocampus (all P<0.03).
Conclusion: Our results show that atrophy of ipsilateral subcortical gray matter structures is part of the disease course of RE. The extent of subcortical atrophy, however, is related to age at onset and the presence of contralateral EEG abnormalities.

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Early inhibition of neuronal chloride uptake for control of neonatal seizure

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Purpose: It is well established that hypoxic ischemic injury induces cytotoxic edema as neurons swell due to the accumulation of water and sodium and potassium chloride salts. *In vitro* data indicate that the chloride accumulation is progressive in both mature and developing neurons and erodes inhibition by changing the direction of the GABAergic currents that subserve synaptic inhibition. Consistent with these processes, seizures become gradually more prevalent and anticonvulsant resistant over the first 24 hours after human neonatal injury. Cation-chloride cotransporters facilitate neuronal chloride accumulation after injury. Combining these key results, we hypothesize that early limitation of neuronal chloride uptake is a uniquely effective anticonvulsant strategy for control of neonatal seizures.
Method: Two-photon fluorescence imaging and non-invasive extracellular field potential recordings were performed in the intact preparation *in vitro* from neonatal mice expressing the Cl^- sensitive fluorescent protein Clomeleon. Spontaneous neuronal network activity, GABA action, cell type-specific Cl^- accumulation were compared under conditions in which NKCC1 inhibitor bumetanide was applied immediately after oxygen-glucose deprivation (OGD) vs

after seizure-like activity was manifested.
Results: We report that: (i) transient OGD progressively increased the neuronal chloride concentration ($[Cl^-]_i$) and inverted the net effect of $GABA_A$ receptor activation from inhibition to excitation. These changes correlate with delayed onset of periodic epileptiform discharges (PEDs), increased frequency of seizures and reduction in phenobarbital efficacy; (ii) the Na^+-K^+-$2Cl^-$ (NKCC1) cotransporter blocker bumetanide more efficiently reduced $[Cl^-]_i$ and depressed PEDs during early vs delayed recovery from OGD; (iii) early and sustained application of bumetanide in combination with phenobarbital prevented seizure-like events.
Conclusion: Our results demonstrate that early block of ongoing neuronal chloride uptake is superior to late block of chloride uptake as measured by control of epileptiform discharges during recovery from OGD. This has direct implications for the timing of clinical interventions such as bumetanide and phenobarbital for neonatal seizures.

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Efficacy of rapamycin in children with drug-resistant epilepsy related to tuberous sclerosis complex

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Purpose: Epilepsy develops in 70–90% of children with Tuberous Sclerosis Complex (TSC) and is often resistant to medication. Given that mTOR overactivation is a hallmark of TSC, mTOR pathway inhibitors are increasingly used for treatment of TSC manifestations, including epilepsy. Everolimus is approved as an added therapy for focal onset seizures in TSC patients. Little is known about the efficacy and safety of mTOR inhibitors in TSC patients with epileptic spasms. Our study evaluated the antiepileptic effect of adjunctive rapamycin in TSC children with drug-resistant epilepsy, including epileptic spasms.
Method: This single center, open-label study evaluated safety and efficacy of at least 12 months of rapamycin treatment in children with drug-resistant epilepsy associated with TSC. Patients with any types of seizures, including epileptic spasms, were eligible.
Results: Forty-two patients aged from 6 months to 16 years were included in the study. In two cases rapamycin was withdrawn due to adverse events (pneumonia and severe stomatitis) and in four cases it was stopped due to lack of efficacy. Thirty-six children received rapamycin for at least 12 months. Eight of them (22.2%) presented with epileptic spasms. Improvement defined as at least 50% reduction in seizure frequency was found in 24 (66.7%) patients, including three patients with epileptic spasms. Seven patients (19.4%) became seizure free, including 2 children with epileptic spasms.
Conclusion: Rapamycin may be a valuable therapeutic option in patients with TSC-associated epilepsy, including children with epileptic spasms.

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Seizure classifications in pediatric SARS-CoV-2 Omicron infection

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Purpose: To analyze different seizure patterns developed in SARS-CoV-2 Omicron BA.2-related encephalitis in children in Taiwan.
Method: We performed a retrospective chart review of all patients who visited the pediatric emergency department of Chang Gung Memory Hospital Linkou branch in the period of April 1, 2022 to July 31, 2022. Cases were defined as children with SARS-CoV-2 infection presenting with fever and seizures, and those with neurological underlying disorders such as epilepsy, congenital central nervous system malformations, metabolic disorders, psychiatric and behavior disorders, previous encephalitis, and taking central nervous system drugs were excluded. The patients were divided into different groups according to their final diagnosis, and the clinical seizure characteristics including presenting aura, semiology including consciousness features, motor phenomena, respiratory dysfunctions, seizure cluster, seizure duration, status epilepticus and post-ictal details were compared.
Results: In this period, 116 patients were enrolled for seizures patterns analysis. Of whom, 14 were diagnosed as acute encephalitis and 102 were diagnosed as non-encephalitic seizures or myoclonic jerks. (66 simple febrile seizures, 16 myoclonic jerks, 15 complex febrile seizures, and 5 febrile seizures plus). There was no presenting aura, and generalized tonic-clonic (GTCs) movements was the most common motor phenomena in all groups. There was no respiratory dysfunction such as hyperventilation or hypoventilation among all groups. Non-encephalitis groups exhibited characterizations including higher level of consciousness, single event seizure without cluster attack, shorter seizure duration, and brief post-ictal period.
Conclusion: Seizure patterns in children infected with SARS-CoV-2 Omicron variant BA.2 present with general tonic-clonic movements as the main motor phenomena. Besides, higher level of consciousness, single event seizure, shorter seizure duration and brief post-ictal period may indicate a lower risk of acute encephalitis.

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Early multichannel EEG analysis in neonatal hypoxic ischaemic encephalopathy: more than just a grade

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Purpose: EEG evaluation supports the identification of encephalopathic neonates that might benefit most from early induced hypothermia. Neonatal EEG grading schemes are mainly focused on general background features of amplitude and continuity. Our aim was to determine the value of more detailed EEG characterization in the early postnatal period to help identify neonates that could benefit most from early intervention.
Method: The earliest hour of EEG (within 12 hours after birth) was analysed in 162 term neonates with HIE, recruited for two multi-centre studies (ClinicalTrials.gov Identifier:NCT02160171 and NCT02431780). We adopted one of the most widely used grading schemes to classify different background grades, and explored its correlation with a short-term outcome measure i.e. the later occurrence of acute symptomatic seizures. We described specific transients and patterns, their distribution among background grades and their correlation with the later occurrence of seizures.
Results: Based on background EEG grading, 66 neonates had mild, 30 moderate, and 66 severe encephalopathic EEG features. Pathological sharps and spikes waves were seen in 38% mild, 57% moderate, 26% severe grade EEGs. Brief pseudorhythmic sequences of sharp-slow wave complexes were seen in 24% mild and 17% moderate EEGs.
In the severe EEG group, a significatively higher rate of later seizure occurrence was found (59%). A lower but still consistent seizure risk was present in the moderate (20%) and mild (12%) EEG groups. Within these latter groups, the presence of spikes and/or pseudorhythmic sequences predicted seizure occurrence with 86% sensitivity and 76% specificity. None of the neonates with evidence of sleep wake cycling in the early EEG developed seizures.
Conclusion: Early background EEG assessment, that includes a more detailed analysis of focal and rhythmic features may be useful in determining the need for treatment in neonatal HIE.

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Intranasal vs buccal vs intramuscular Midazolam for the home and emergency treatment of acute seizures in pediatric Egyptian patients

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Purpose: We wished to compare the efficacy, ease of administration and overall satisfaction of midazolam by the buccal, intranasal or intramuscular route in the treatment of acute seizures in Egyptian children both at homes and Emergency department
Method: : A prospective, randomized, trial was performed in children aged 1 months to 17 years with acute seizures lasting longer than 5 min. Children were randomly assigned to receive midazolam, 0.2 mg/kg, by the buccal, intranasal or intramuscular route. The primary

endpoint was seizure cessation within 10 min of drug administration and no seizure recurrence within 30 minutes.
Results: There were 196 seizures analysed in home group , 67 patients received midazolam via \buccal route, 60 via intranasal , 69 via intramuscular route while 105 patients were recruited from ER 37 patients received buccal midazolam, 34 received intranasal and 34received intramuscular midazolam. Intramuscular midazolam stopped seizures within 10 min in 94.2 % in home group and 85.3 % in ER group. on the other hand, intranasal midazolam was successful to stop seizures in 93.3% in home group and 88.2 % in ER group within 10 minutes. and the buccal route was effective in 91% in home group and 78.4 % in ER group. There were no significant difference in efficacy between all groups. Time to seizure cesstion was significantly higher in the buccal group. Highest overall satisfaction and ease of administration was seen in intranasal group especially among caretakers in home group. Intramuscular midazolam was more preferred by physicians in er group. There were no significant cardio-respiratory events in all groups.
Conclusion: Our results indicate that there is no clinically important difference between buccal, intranasal and IM routes of administration midazolam. Buccal, intranasal and intramuscular midazolam were safe and effective for treatment of acute seizures in children.

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Epilepsy with eyelid myoclonias - a diagnosis concealed in other genetic generalized epilepsies with photoparoxysmal response

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Purpose: Epilepsy with eyelid myoclonias(EMA) is a genetic generalized epilepsy (GGE) characterized by eyelid myoclonia, eye-closure sensitivity and photosensitivity. Data on EMA patients who specifically present with photoparoxysmal response on EEG is lacking. EMA is an under-recognized syndrome which is frequently misclassified as another GGE. The main objective of our research is to describe the occurrence of EMA versus other
GGEs among patients with photoparoxysmal response and evaluate their distinguishing features.
Method: We retrospectively identified all patients who had photoparoxysmal response on EEGs performed at Cleveland clinic between 01/01/2012 and 12/31/2019. Initial epilepsy diagnosis and clinical data were collected. EEGs were reviewed for eyelid myoclonia and eye-closure-sensitivity which were used as main diagnostic clues for EMA. If clinical criteria was met, diagnosis was revised as EMA.
Results: Of 249 patients with photoparoxysmal response, 70(28.1%) met EMA criteria. Sixty-two (88.6%) were females. Mean age of onset of epilepsy was 7 years (+7.9) and 120(48.2%) had other GGEs. Fifty-four (77.1%) patients with EMA were initially classified as

another epilepsy. Initial diagnosis included CAE or JME in 40 (57.1%) patients with EMA so we compared EMA with these syndromes. Female preponderance, drug refractoriness, older age of onset and generalized myoclonia were more common in EMA than CAE. Earlier age of onset, absence seizures, and lack of generalized myoclonic jerks were more common EMA than JME.
Conclusion: Our study demonstrates that EMA is under-recognized among GGE patients with photoparoxysmal response. It highlights distinguishing clinical and electrographic features which separate EMA from other GGEs.
It emphasizes the diverse treatments utilized and the need for therapeutic options for patients with refractory EMA.

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Experience of early discontinuation of medication in acute symptomatic neonatal seizures

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Purpose: Neonatal acute symptomatic seizures are usually self-limited and normally remit within the first 72 hours. Despite this, many patients continue treatment for months or year. There is no evidence that maintaining treatment prevents epilepsy. We present our experience in term newborns with symptomatic seizures secondary to hypoxic-ischemic encephalopathy (HIE) and stroke (most frequent etiologies).
Method: All patients admitted between 2018 and 2021 in the NICU with seizures secondary to HIE and stroke were enrolled in a descriptive retrospective study. We describe the treatments used, response rate, time of medication withdrawal and recurrence of seizures at one year follow-up.
Results: We included 51 patients (26 stroke; 25 HIE). Phenobarbital was the drug of first choice in 49/51 patients.
38/51 required a second treatment, which was levetiracetam in 78.9%.
On discharge from the NICU, seizure control was achieved in 46/51 patients (3 deaths). Medication withdrawal before discharge from the NICU occurred in 17/46 patients (37%), with a median of 23 days of treatment (range 0-35 days). In the other 29 patient, treatment was continued during follow up (96.5% with levetiracetam), for a median time of 92 (range 60-124) days since discharge.
Seizures recurrence was seen during the first year of life in 5/45 patients (11.1%), 2 with refractory epilepsy. No differences were observed in seizures recurrence between the patients whose antiseizures treatment was withdrawn before discharge or during follow-up. In fact, of the 5 patients who relapsed, 4 belonged to the group that maintained the treatment upon discharge from the NICU.
Conclusion: Recent studies and our results support that there are no differences in seizure recurrence in patients who interrupted treatment before discharge compared to those who

maintained it. This supports early withdrawal of medication safely for most patients with acute symptomatic neonatal seizures.

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Prospective 5 year longitudinal study detects neuro-cognitive and imaging correlates of seizure remission in self-limiting Rolandic epilepsy

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Purpose: Self-limiting Rolandic epilepsy (RE) is one of the most common epilepsies in school-age children. Seizures are generally infrequent, but cognitive, language, and motor coordination problems can significantly impact the child's life. To better understand the changes in brain structure and neurocognitive function in RE, we longitudinally assessed neurocognition, cortical thickness and sub-cortical volumes.
Method: At baseline, we recruited 30 participants diagnosed with RE and 24 healthy controls and followed up for 4.94 ± 0.8 years after baseline when the participants with RE were in seizure remission. Measures included: T1-weighted magnetic resonance brain imaging (MRI) with Freesurfer analysis and a detailed neuropsychological assessments.
Results: Longitudinal MRI revealed excess cortical thinning in the left orbitofrontal ($p= 0.0001$) and pre-central gyrus ($p= 0.044$) and an increase in right putamen volume ($p =0.003$) in individuals with RE compared to age-matched healthy controls. Longitudinal neuropsychology revealed significant improvements in the symptoms of developmental coordination disorder (DCD, $p = 0.005$) in seizure remission. Excess decline in fluid intelligence in RE compared to controls and improvements in a component of auditory processing in the RE group did not reach significance threshold after multiple testing adjustment.
Conclusion: There is longitudinal evidence for altered development of neocortical and dorsal striatal regions between active Rolandic epilepsy and seizure remission, predominantly within two clusters maximal in the left-orbitofrontal and pre-central gyrus as well as the right putamen. Changes in brain structure possibly represent a candidate marker of motor function associated with seizure remission. There is significant evidence for improvement in motor coordination between active seizures and seizure remission and suggestive evidence for a decline in fluid intelligence and gains in auditory processing.

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Quantitative EEG parameters in childhood epileptic encephalopathy and childhood neurodevelopmental disorders

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Purpose: Despite quantitative EEG(Q-EEG) not having same widespread use as conventional EEG, it can provide a rapid diagnosis of epileptic seizures and differential diagnosis between various subtypes. Role of Q-EEG in the evaluation of neurodevelopmental disorders like Autism Spectrum Disorders(ASD) with/without epilepsy has not been well studied. The Q-EEG parameters(spectral power and spectral coherence) were studied in children of two groups[epileptic encephalopathy(West Syndrome) group & neurodevelopmental disorders(ASD with/without epilepsy) group]
Method: Ten children with West Syndrome, 64 children with ASD, 11 ASD children with epilepsy(ASD-E) and 50 typically developing children were studied. Baseline demographic and clinical characteristics were recorded in all subjects. Q-EEG was recorded from 128 electrodes using an Electrical Geodesics(EGI) high-density EEG system(Netstation). In the West Syndrome group, the Q-EEG was repeated after 3 months of hormonal therapy.
Results: Among 10 children with West Syndrome, 50% did not respond to hormonal therapy. A higher delta-power was observed in non-responders, which was not statistically significant. There was no significant difference in power spectral density for the five-frequency band which was analysed among responders and non-responders. Among the ASD, ASD-E and control groups, it was found that the spectral power of gamma(γ), beta(β), lower alpha1(lα1), theta(θ) and coherence of γ, lα1, during eyes-closed condition was significantly($p<0.0005$) lower & the spectral power of θ & coherence of lα1, θ, δ, was significantly lower($p<0.0005$) during eyes-open condition in ASD compared to typically developing children. Children with ASD had impairment in cortical areas involved in tactile-perception and language-processing while the ASDE group also had additional impairment in pathway responsible for orientation and location of objects.
Conclusion: Q-EEG represents a useful tool to improve clinical diagnosis and treatment response evaluation, in children with epileptic encephalopathies as well as in neurodevelopmental disorders. However, further studies are required to use Q-EEG in clinical practice for the management of these disorders.

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Electroencephalogram (EEG) and alternating hemiplegia of childhood (AHC): a prospective and retrospective EEG study of a large cohort of 32 patients

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Purpose: Alternating hemiplegia of childhood is an early encephalopathy, associating paroxysmal hemiplegia/dystonia episodes, and often epilepsy. Currently there is no publication exclusively dedicated to EEG aspects during and/or outside paroxysmal events. We aimed to describe and analyse EEG presentation not only during epileptic seizures, but also during alternating hemiplegias, paroxysmal dystonias and other neurological accesses.
Method: 32 consecutive patients with AHC were included in the study and their EEGs, mostly of long duration (24 hours, n=29) were read by two electro-physiologists. A third electro-physiologist was consulted and undertook a third lecture in case of important conflict in the comparison of the two interpretations or in case of new, particular, and unique EEG patterns.
Results: Ten patients (31%) had an abnormal background activity. Twenty one of them (~65%) had focal abnormalities and four had generalized. Of the seven EEGs with hemiplegic seizures, two had contralateral slow waves and one ipsilateral. Six EEGs with dystonic seizures were seen and one presented an unusual homolateral occipital pattern during the event. In the four patients where paroxysmal eye movements were recorded, no electrical correlate was found. For six patients we recorded epileptic seizures (focal, atonic, tonic, generalized, dysautonomic, status epilepticus), two of them with unusual patterns of extremely slow discharge progression. Other unusual patterns were prolonged unilateral slow waves (n=6), during sleep, and pseudo-periodic waves (n=4) outside or in the period preceding or following paroxysmal events. Five patients presented dysautonomic, non-epileptic episodes (brady-, tachy-cardia, desaturations).
Conclusion: At present, there are extremely few EEG studies available on AHC. They highlight a sometimes slow background rhythm, and some episodes of hemiplegia are collected, without uniform/characteristic pattern. Recently, changes in the EEG spectral analysis before the plegic access have been reported. We confirm previous observations and describe new and extremely unusual EEG patterns of complex interpretation.

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Patient-driven collaborative approach to address the challenges that hinder therapy development in Dravet syndrome

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Purpose: Dravet syndrome (DS) is a rapidly and promisingly advancing field where, however,

many unmet needs remain, for example, the impact of comorbidities on quality of life, the lack of knowledge and standards of care for DS in adulthood, or the lack of outcome measures that reflect the full spectrum of the disease. In such a context, competition, duplication of effort, and lack of consensus on a prioritized list of research questions, pose potential threats to the field and risk delaying time to new and more effective treatments.
We showcase an innovative model to engage a variety of stakeholders in a focused conversation aiming at developing a research roadmap for DS. The initiative was sponsored by Gruppo Famiglie Dravet - Italy, Vereinigung Dravet Syndrom Schweiz – Switzerland, and Dravet Syndrom e.V. – Germany.
Method: The work started out with a DS landscape analysis including the state of DS research, therapeutic pipeline, availability of translational research infrastructures, etc. Scientific publications on the subject matters were extracted from both Scopus and PubMed. Insights gathered from interviews with international experts were also included. The ensuing landscape document was then used as a platform to facilitate discussion among several stakeholders which took place in January 2023, during two virtual roundtables with patient's representatives, clinicians, basic investigators, industries and the regulatory agency.
Results: During the two workshops, participating stakeholders reflected together around a number of open questions and arrived at some recommendations that will form the research roadmap
Conclusion: We describe an innovative model to engage a variety of stakeholders in a focused conversation to optimize research priorities and dynamics. It provides a framework for patients to become effective partners in research.

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Localizing and prognostic value of pre-surgical interictal epileptiform discharges in pediatric patients with ganglioglioma related epilepsy – a pilot study.

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Purpose: The localizing value of interictal epileptiform discharges (iEDs) in context with radiologically confirmed tumor localization and their prognostic significance for post-surgical seizure outcomes in ganglioglioma-associated epilepsy are unclear/controversial.
We retrospectively investigated consecutive pre-surgical non-invasive video-EEG monitorings of children and adolescents operated at our center for histo-pathologically confirmed epilepsy-associated gangliogliomas (WHO I).
Method: Pre-operative scalp Video-EEG-monitorings were reviewed independently by two board-certified neurophysiologists, blinded to pre-operative neuroimaging results. Frequency, morphology, and localization of iEDs during both wakefulness and sleep were assessed, and concordance with pre- and postoperative MRI findings, surgical reports and surgical out-

comes was evaluated. Significance level was set at $p < 0.05\%$.
Results: 188 days of preoperative video-EEG-Monitorings recorded in 32 patients (15 female, 16 male) were analyzed so far. Median age at surgery was 6,5 (IQR, 2,8-13,5) and median duration of epilepsy 1,7 (IQR, 0,8-3) years. Median follow up after surgery was 36 (IQR, 23-84) months with 22 (71%) patients attaining a favorable seizure outcome (ILAE Class I). IEDs were detected during wakefulness in 18 (42%), during sleep in 29 (94%) and not detectable in 2 (6,5%) patients. IED-to-tumor localization was concordant in 21 (ipsilobar: 61,3%, ipsihemispheric: 6,5%) and dis-concordant in 8 (bilateral and multiregional: 19,4%, mirror spikes: 6,5%) cases. In a binary backward stepwise logistic regression model, the presence of ipsilobar and ipsihemispheric iEDs was significantly (OR 9,0, CI 1,6-52,3, p=.014) associated with favorable (ILAE Class = I) surgical seizure outcomes.
Conclusion: Provided that a prolonged sleep recording with at least stage II sleep was obtained, iEDs of-high localizing value could be detected in a majority of pediatric patients with ganglioglioma related epilepsy. An ipsilobar or ipsihemispheric iED-to-tumor localization was associated with favorable surgical seizure outcomes.

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Post-ictal epileptic spasms: an electro-clinical phenomenon associated with structural lesions and treatment-resistant epilepsy.

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Purpose: Epileptic spasms can sometimes occur outside Infantile epileptic spasms syndrome, but these are poorly described. These are often seen in the context of other seizures, particularly in the postictal phase but the clinical relevance of this phenomenon is unclear. The aim of this study was to characterise clinical presentations and EEG features of so-called post-ictal spasms.
Method: The local database of the Clinical Neurophysiology Department of Great Ormand Street for Children (GOSH) was searched for spasms in the context of other seizures in the period of between 2004 to 2019. Inclusion criteria: spasms in the context of other seizure types and at least one cluster of spasms captured on EEG monitoring. Exclusion criteria were no temporal relationship to other seizure types, the semiology and EEG features not concordant with epileptic spasms. EEG polygraphy and video data were independently reviewed by 2 reviewers.
Results: Of 250 patients with spasms, 18 met all inclusion and exclusion criteria. Most were male (15/18) and the mean age was 7 years. All 18 patients had complex structural brain abnormalities with 7 having tuberous sclerosis. All had drug-resistant epilepsy. The preceding seizure types included focal unaware seizures, focal seizures with behavioral arrest and focal

tonic seizures. The majority of spasms involved deltoids (13/18) with EMG activation during the spasms, 4/18 had facial spasms, and 14/18 had spasms of the limbs. EEG features and semiology were similar to those seen in infants. The mean duration of time from seizure end to spasm cluster start was 4 seconds. The duration of the cluster was variable from 10 sec to several minutes, but spasms were all self-limited.
Conclusion: Epileptic spasms may occur in the context of other, typically in the postictal phase. This phenomenon is mostly seen in children with complex drug-resistant epilepsy.

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Systematic review of the genetics of FCD

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Purpose: A significant number of patients with focal epilepsy are due to focal cortical dysplasia (FCD), in recent years, several publications have demonstrated that in a high percentage of cases, genetic variants can be found in FCD.
Method: A scoping review of the literature was conducted according to previously described methods and the PRISMA Checklist. A comprehensive search strategy was applied in PubMed, Embase, and Scielo in October 2022. We did not filter by year of publication. References were screened based on title and abstract, and posteriorly full-text articles were assessed for inclusion according to eligibility criteria. Studies referring to the diagnosis of FCD type I, II, or III according to Palmini's or the ILAE classification system were included. Data were extracted and summarized for an overview of the evidence.
Results: Our search identified 269 references, but only 44 studies were included in our review. Publications have increased dramatically in the last decade and several of the most recent studies have focused on a genotype/phenotype correlation and have described many variants not previously related to FCD. Type I FCD exact genetic cause still remains elusive due to low sample numbers, in comparison to type II. Nonetheless, a significant proportion of patients in different cohorts proved to be affected by at least one germline variant. On the other hand, most FCD type II patients harbored somatic variants, in many cases preceded by a germline variant, supporting the two-hit model proposed a few years back.
Conclusion: Growing evidence supports that FCD can be secondary to genetic variants, but the evidence shows that genetic mechanisms behind them are most likely complex, requiring a individualized approach, rather than one size fits all. The new ILAE classification system would help standardize terminology and future research.

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DEP score – a simple bedside tool to diagnose psychogenic non-epileptic seizures

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Purpose: As of today, efficient bedside tools for differentiating psychogenic non-epileptic seizures (PNES) from epileptic seizures (ES) haven't been found. The study aimed to build and validate a clinical tool that will allow a good differentiation between PNES and ES.
Method: We constructed a 4-dimensional scale that included: 1. The absence of global dynamics of the movement type 2. The absence of global dynamics of the movement rhythms. 3. Eyes closure during an event. 4. The absence of rotational pelvic movements.
Each dimension received a score of 1- if it met the above conditions or 0- if not. The total score ranged from 0-4. The score was named DEP (Dynamics of movements, Eyes closure, and Pelvic rotation).
Two junior residents in their first months of residency underwent practice on a series of video footage that we had used in a previous study. Subsequently, each rater was given 20 video footage and had to score each case.
We hypothesized that a low score would indicate an ES attack, and a high score would indicate a PNES attack.
Results: Intraclass correlation between raters was high (r=.87). The ES group (M=0.80, SD=1.11) was rated lower compared to the PNES group (M=2.95, SD=0.76) ($t(18)=5.05$, $p<.01$). A ROC analysis showed a statistically significant AUC (.93). Youden index J showed a 90% sensitivity and 80% specificity for a 1.5 score cutoff.
Conclusion: High DEP score >1.5 has high sensitivity and specificity for PNES diagnosis and can serve as a simple bedside tool for PNES diagnosis.

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Prevalence of ictal injuries in functional (psychogenic nonepileptic) seizures: a systematic review and meta-analysis

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Purpose: A systematic review and meta-analyses were conducted to assess the prevalence of wounds and injuries resulting from functional seizures (FS; psychogenic nonepileptic seizures) in adults.
Method: A literature search was performed in PubMed, Embase, LILACS, Scopus, Web of Science, PsycINFO, Google Scholar, OpenGrey, and ProQuest. Observational studies were included. The risk of bias was assessed using the Joanna Briggs Institute critical appraisal checklist for studies reporting prevalence data. The software RStudio was used to perform meta-analyses. Cumulative evidence was assessed according to GRADE criteria.

Results: From the 2,607 identified records, 41 studies were included in the qualitative synthesis, and 28 in meta-analyses (six studies were used twice because two types of prevalence were reported). A meta-analysis of 13 studies (1,623 individuals were included), resulted in an overall lifetime prevalence of injuries due to FS per person of 25% (95% CI 19%-32%; I^2 = 88%). In contrast, considering a limited period (VEEG monitoring days), a meta-analysis of 13 studies (844 individuals), resulted in an injury prevalence due to FS per person of 0.7% (95% CI 0%-3%; I^2 = 73%). In addition, a meta-analysis of 8 studies (1,000 individuals), resulted in an overall period prevalence of injuries per FS event of 0% (95% CI 0%-0.4%; I^2 = 49%). The certainty of cumulative evidence assessed by GRADE was rated "very low" for lifetime prevalence of injuries per person, "low" for period prevalence per person, and "moderate" for period prevalence per number of FS.
Conclusion: Overall pooled lifetime prevalence of injuries due to FS per person was 25%, while the period prevalence of injuries per person and per seizure was more negligible (0.7% and 0%, consecutively). Awareness of the frequency of these injuries among healthcare providers might improve the management of FS.

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Psychogenic non-epileptic seizures in adults with intellectual disability: a matched case-control study in all inpatients living in tertiary epilepsy centres in the Netherlands

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Purpose: To describe the characteristics of psychogenic nonepileptic seizures (PNES) in adults with epilepsy and intellectual disability (ID), and to analyse differences regarding psychosocial functioning and epilepsy severity between individuals with and without PNES.
Method: Medical records of 540 inpatients with ID and living at epilepsy care facilities in the Netherlands were screened for PNES and evaluated by a neurologist. A control group consisting of subjects with epilepsy and ID, without PNES, was matched according to age, sex and level of ID. Characteristics of PNES, epilepsy and psychosocial functioning were provided by the subject's nursing staff, retrieved from patient charts or collected by standardized questionnaires.
Results: In total, 35 cases and 35 controls were included. The point prevalence of PNES was 7.8%. The subjects with PNES were most often females, had a mild or moderate level of ID, showed higher levels of depressive symptoms, anxiety and self-injurious behavior and experienced significant more negative life events in the past 12 months. The amount of negative life-events was the biggest predictor of developing PNES. Stress-related triggers were recognised in a large majority.
Conclusion: People with both intellectual disabilities and epilepsy who are encountered with negative life events appear to be more vulnerable to PNES. Although no causal conclusions can be drawn, the higher levels of depressive symptoms, anxiety and self-injurious behaviour

in people with ID, epilepsy and PNES suggest that even in inpatient care the impact of negative life events seems underexposed. This study could therefore have implications for diagnosis and treatment in this specific population.

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Disparities in health outcomes in Medicaid patients with epilepsy by practice setting: promoting health equity in American academic medical centers

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Purpose: In American academic medical centers, patients covered by Medicaid can receive care in a separate facility than those not covered by Medicaid. In 2018, the Neurology Department at Mount Sinai Hospital adopted integration of care; the non-Medicaid 'faculty practice' could now see patients who would previously only be eligible for the Medicaid-only 'outpatient clinic.' We aimed to evaluate the association between facility type (integrated or not) and telehealth utilization.
Method: We performed retrospective analyses using the Mount Sinai Health System (MSHS) electronic medical record data. We identified people of all ages with epilepsy who were followed by an epileptologist after 2018 using an ICD-10-CM coded case definition validated in our health system. We computed descriptive statistics and evaluated associations between practice setting and telehealth utilization using logistic regression.
Results: We evaluated three sub-groups in our sample (N=4586): (1) Medicaid patients seen in Medicaid clinic (N=387), (2) Medicaid patients seen in outpatient practice after integration (N=723), and (3) non-Medicaid patients seen in outpatient practice (N=3476). Patients in group 3 were significantly older than Medicaid patients, with an average age of 40 compared to 29 and 28.5 in groups 1 and 2 respectively ($p<0.0001$). Medicaid patients were more likely to have drug resistant epilepsy, with 51.94% of patients in group 1, 41.63% in group 2, and 37.2% in group 3 having drug resistant epilepsy ($p<0.0001$). Medicaid clinic patients were less likely to have telehealth visits (phone and video); 81.65% of patients in group 1 had no telehealth visits compared to 71.78% in group 2 and 70.89% in group 3 ($p<0.001$).
Conclusion: We found higher telehealth utilization in those followed in the integrated faculty practice, suggesting that integrated care may be associated with better health outcomes in people with epilepsy. Future research should examine the direct impact of integrated care on other epilepsy related health outcomes.

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Using community-university partnerships to implement WHO's Intersectoral Global Action Plan on Epilepsy and Other Neurological Disorders (IGAP) 2022-2031: an example focusing on mental health in epilepsy

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Purpose: In 2022, WHO's Member States approved an Intersectoral Global Action Plan on Epilepsy and other Neurological Disorders (IGAP), endorsing a comprehensive, coordinated, intersectoral response to reduce gaps in epilepsy knowledge and treatment. Given the importance of IGAP implementation, we aim to illustrate how partnerships between community agencies and academic researchers can accelerate uptake of evidence-based programming to improve mental health in people with epilepsy.
Method: Academic researchers were approached by a community epilepsy agency about the need for an intervention to reduce stress and manage emotions and behaviors among children with epilepsy and parents. Together we delivered and evaluated a mindfulness-based parent and child program designed to improve mental health. We assessed feasibility of interactive online delivery by agency staff to enable scaling up delivery across our region and beyond.
Results: We executed a randomized controlled feasibility trial with 73 child-parent dyads. Benefits and challenges were documented from the perspectives of community agency and researchers. We identified two key mutual benefits: our research directly addresses a community-identified need to foster mental health in children with epilepsy and parents, and funding is easier to secure due to our effective partnership. Challenges for the community partner include time required to learn and execute research processes. Challenges for researchers include innovation and flexibility required to design interventions for integration into agency operations given limited resources. We will present specific lessons regarding key facilitators for success.
Conclusion: This intersectoral partnership between a community epilepsy agency and an interdisciplinary team of researchers demonstrates one example of implementing the IGAP's Strategic Objective 5: Strengthen the public health approach to epilepsy. We articulate specific facilitators to overcome barriers to achieve IGAP's 148 (d) "conduct implementation research, including the dissemination of lessons learned to accelerate the scale-up of successful strategies to strengthen epilepsy services".

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EpilepsyPOWER: preliminary results of a multicenter European project

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Purpose: Employment is a pivotal factor of social integration, especially for people with epilepsy (PwE). Despite good seizure control, about 25% of PwE remain unemployed for several reasons, including stigma and misconceptions about epilepsy. The EpilepsyPOWER is a European project, financed by the programme Erasmus+, involving five European Countries (Italy, Bulgaria, France, Ireland, Germany), aimed to improve the workplace inclusion chances of PwE in Europe. We created surveys to explore employment condition in European PwE, focusing especially on disclosure, seizures and stigma.
Method: We have developed anonymous surveys for PwE on SurveyMonkey software. We shared personal links to surveys through email addresses. At now, we have collected a total of 201 answers (112 from Bulgary, 85 from Italy and 4 from Germany). Surveys included questions about demographic factors, clinical features, employment and education, stigma and disclosure in workplace.
Results: Among our respondents, 8% were unemployed, 56% were employed in a part-time or full-time job, 11% were students, 10% was in receipt of a disability allowance, 15% declared other employment status. A total of 38% PwE experienced almost one seizure at work. About 24% of PwE declared to experience difficulties with colleagues and/or employers in the workplace; of those, 75% attributed those challenges to epilepsy. A total of 31% PwE declared that stigma could impact negatively on finding and retaining a job and 50% thought that epilepsy could represent an obstacle in finding a job. As for disclosure: 32% of PwE revealed their condition, 8% revealed epilepsy only to colleagues and 13% only to employers, whereas 38% did not disclose their disorder.
Conclusion: Our study demonstrated that stigmatization and disclosure still stand as issues for PwE in the workplace. Exploring PwE work conditions with our surveys could help in providing information to employers about epilepsy and reduce the rate of unemployment among PwE.

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Neurocognitive and psychosocial issues in adults with newly diagnosed epilepsy - a systematic review

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Purpose: It has been recognized that, in the management of individuals with epilepsy, careful consideration should be given to cognitive problems, psychiatric comorbidities and a wide range of psychosocial challenges (e.g., stigma, relationships) that often emerge at an early stage of the diagnosis. Healthy adaptation to the diagnosis and management of epilepsy at an early stage may significantly impact long-term medical and psychosocial outcomes. Access to necessary and sufficient information about epilepsy, including the risks and the appropriate ways to manage and cope with complications along the disease course is critical.
Method: The focus of this systematic review is to provide a structured evaluation of the literature on the psychosocial and neurocognitive outcomes in adults (18-65 years) with newly diagnosed epilepsy (diagnosis within 24 months). We adopted an inclusive approach to define psychosocial and neurocognitive parameters, and included search terms related to quality of life, psychiatric comorbidities, social functions, self-perceptions and neurocognitive sequelae. We conducted electronic searches of the Medline, Web of Science, PsycInfo and CINAHL databases from their inception years to 2022 and hand searched high impact journals with relevance to epilepsy research. PRISMA standards were adopted.
Results: In total, 660 articles were identified. After screening abstracts and removing duplicates, 96 articles were selected for further review. Of these, 24 (25%) are randomized controlled trials. Eighty (83%) were conducted in developed countries, while 16 (17%) were conducted in developing countries. A range of themes and approaches to the management of the comorbidities are identified, including few interventional studies, and will be further examined and described upon full text review.
Conclusion: Preliminary results showed that there is a paucity of global research aimed at identifying and managing neurocognitive and psychosocial outcomes in the early stages following epilepsy diagnosis. Findings from this review will have important clinical implications and recommendations for further studies.

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Adapting PACES in epilepsy: multi-phase process with Spanish-speaking adults with epilepsy

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Purpose: The Program for Active Consumer Engagement in Self-management (PACES), an 8-week, professional and peer-lead, group-based program, was created and validated with English-speaking PWE. RCT data showed immediate and long-term effects on depression,

epilepsy self-management (ESM) and self-efficacy, and QoL. Minimal ESM research to date has prioritized Hispanic PWE, despite disparities. This needs assessment study was done to culturally and linguistically adapt PACES program content, format and delivery.
Method: English PACES materials were forward and back translated; subsequently verified by bilingual, bicultural epilepsy clinician-researchers. Next, Spanish PACES program and materials were presented to separate focus groups of Spanish-speaking PWE and Spanish-speaking epileptologists. Patient groups' quantitative (Likert-scaled ratings) and qualitative (open-ended queries) data validated content.
A needs assessment survey was implemented to quantify Spanish-speaking patient's perceived epilepsy-related problems and opinions and treatment needs.
Results: Spanish-speaking PWE completed 100 mailed surveys (30% response rate). Respondents were =45.4 years old; 57% male; 90% from Mexico; living in the United States 25-years. Results were compared to previously surveyed English-speaking PWE. Mann-Whitney tests comparing Spanish- and English-speaking patient responses were not statistically different. Spanish-speaking patients prioritized web or phone format, yet 52% do not know how to use the internet despite high cell phone possession (81%). Other delivery preferences were non-different. There was a significantly stronger preference for a psychologist as the PACES interventionist, there was a lower preference for help with coping skill development (the relative priority being education only).
Conclusion: Original PACES content and structure was supported by Spanish-speaking PWE. Data indicate relevance of telehealth delivery by a Spanish-speaking psychologist and peer facilitator dyad. Data do not suggest new needs (e.g., vocational), nor nullify existing content. Although not queried directly, patients demonstrated a preference to have family; forthcoming RCT will include this aspect.

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Epidemiology of epilepsy in Colombia: Prevalence, distribution and association with stroke, trauma, and dementia

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Purpose: Epilepsy represents an important burden on healthcare delivery in Colombia. Acquired epilepsy is commonly related to stroke, trauma or dementia in adults. The Colombian health system has implemented SISPRO, a national health registry gathering information from the National Health System. It covers approximately 95% of the Colombian population. Registries can present information about access to prompt and accurate neurological diagnosis. The aim of this research is to describe the prevalence and distribution of epilepsy in Colombia and relate its diagnosis with the diagnosis of stroke, trauma and dementia based on national data.
Method: This is a descriptive epidemiological study. Data was collected by SISPRO to esti-

mate prevalence and characterise patients diagnosed with epilepsy. We included all types of epilepsy in people from 0 to 99 years registered from January 2017 to December 2021. Prevalence of all conditions was calculated for 1000 habitants. Prevalence ratio was calculated dividing the prevalence of epilepsy in people with trauma, stroke or dementia by the prevalence of epilepsy in general population. For stroke and dementia, prevalence ratio was estimated in population >50 years-old.
Results: National prevalence is 8.5 per 1000 habitants. The highest prevalence was found in Quindío department. In women we found a bymodal presentation, peaking at 19 and 52 years old. In men, the peak of prevalence was reached at 19 years-old. Prevalence ratio with stroke is 5.4, peaking at the age group of 70-74 years-old. Prevalence ratio with dementia is 4.4, being highest in the youngest patients. Prevalence ratio with trauma is 2.6, being highest in the age group between 0-4 years old.
Conclusion: Colombia reported a lower prevalence of epilepsy compared with global and regional registries. Trauma, especially in younger people, as well as stroke and dementia in the elderly, are statistically associated with a higher risk of epilepsy in Colombia using real-world data.

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Job security of people with epilepsy

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Purpose: Epilepsy has negative effects on socioeconomic status for the patients. The negative consequences result not only from actual disability because of recurrent attacks, but also from stigma. We aimed to investigate whether a diagnosis of epilepsy has an impact on their job security.
Method: We conducted a nationwide population-based retrospective cohort study using the Korean National Health Insurance Service database. We included newly diagnosed 25 to 54 year-old people with epilepsy (PWE), ascertained by diagnostic codes and anti-seizure medication (ASM) prescriptions, who were in employed status at the diagnosis of epilepsy between January 2007 and December 2018. Factors associated with job loss and re-employment were investigated.
Results: Among 13,122 newly diagnosed PWE, 2,852 (21.7%) and 6,407 (48.8%) lose their job within one year and overall follow-up period (mean 4.11, standard deviation 3.59 years) respectively. When adjusted for age, sex, type of industry and income level, greater the number of ASM tried (adjusted hazard ratio, aHR=1.33 for ASM≥4), number of ER visits or hospitalization (aHR=3.73 for visits≥2), and central nervous system (CNS) (aHR=1.14) and psychiatric (aHR=1.19) comorbidity were associated with job loss. Among 2,572 who lost their job within the first year and were followed up for one or more year, 1,184 (46.0%) were re-employed

during follow-up (mean 3.99 standard deviation 3.45 years). Number of ASM tried (aHR=0.73 for ASM≥4) and number of ER visits or hospitalization (aHR=0.32 for visits≥2) and CNS disease (aHR=0.71) were negatively associated with re-employment.
Conclusion: Job loss rate was 1.3 to 1.7 times higher in PWE within the first year after diagnosis than in general population and tended to decrease over time. Poor disease control and comorbidities were associated with job loss. As well as active control of seizure, social support program to stabilize employment after diagnosis of epilepsy is needed.

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Reducing risk and enhancing care by developing an Irish consultation guide for people with epilepsy (PWE) and family physicians (GPs)

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Purpose: To assess the feasibility of implementing a patient-held guide in Irish GP settings, determining important aspects in the care of PWE that should be addressed by GPs, and informing the development of a guide that would be satisfactory to GPs
Method: Using a qualitative study design, this research was a collaboration with an academic department of general practice and a national patient organisation, Epilepsy Ireland. People with Epilepsy (PWE) were recruited through EI staff. GP participants were recruited by convenience sampling from different geographical areas. One-on-one semi-structured interviews were conducted, audio-recorded, transcribed verbatim. Thematic analysis was applied to identify significant themes. Twenty-one interviews were conducted. Transcripts were thematically analysed and coded for nodes and relationships.
Results: Thematic saturation was achieved after interviewing 11 PWE and 10 GPs. 4 themes precipitated: perceived limited role of GPs in epilepsy care; lack of consistency; limited epilepsy knowledge; and enthusiasm for a guide to enhance clinical interaction. Participants were also asked to identify the key features, the perceived benefits and drawbacks of a consultation guide. Advantages included: patient-centred communication continuity of care. The perceived drawbacks were loss of a physical guide, low patient enrolment and time limitations. Preferred guide content included: seizure history, medication, self-management, mental health, safety and women's health.
Conclusion: Based on opinions gathered from PWE and GPs, developing a patient-held guide in Irish primary care is an acceptable and valuable endeavour. The findings in this study inform content and purpose of a consultation guide in general practice, providing a more accessible and informed platform to reduce risk and enhance quality of life. This can improve

access to advice and support for people with epilepsy to enhance self-management of the condition and reduce risk from poor adherence and low mood.

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Supporting families affected by childhood epilepsy beyond the clinic walls

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Purpose: Having experienced the loss of social interaction, the disintegration of support networks, and limited access to in-person education during COVID-19, families affected by childhood epilepsy felt anxious about re-engaging with the outside world. They expressed the need to re-connect with others in a similar situation but recognised the barriers and challenges they faced. We aimed to create safe, welcoming environments for young people with epilepsy, and help them build the confidence to engage with their peers in education, social, and leisure activities.
Method: We redeveloped our Seizure Smart epilepsy awareness sessions for schools' communities to allow for COVID-safe delivery, including delivery in playgrounds.
We contributed epilepsy awareness education in-person and online to public events with a target audience of young people e.g., *Curious About the Body* at Glasgow Science Centre.
We offered young people with epilepsy and their families the chance to try challenging outdoor activities in a group setting.
Results: Between September 2021 – September 2022:
More than 10,000 young people had access to positive messages about epilepsy and tips on how to help someone having a seizure.
49 young people with epilepsy and their families enjoyed residential trips to Ardentinny Outdoor Education Centre, Argyll, Scotland, where they enjoyed canoeing, climbing, gorge-walking, night forest walks, and team challenges.
Conclusion: Epilepsy awareness education is popular with young learners and teachers and contributes to the delivery of several strands of the Scottish curriculum.
Families value supportive, inclusive breaks and report that the benefits include feeling more confident, enjoying a much-needed break from their usual routine after years of restrictions, reconnecting with others, and rebuilding informal peer support networks.
The ongoing impact of COVID-19 continues to restrict opportunities for families affected by childhood epilepsy to engage.

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Participatory policy making by World Health Organisation (WHO): case study - inclusion of persons with epilepsy in the Intersectoral Global Action Plan on Epilepsy and Neurological Disorder (IGAP) development

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Purpose: In policy development, lived experience participation in policy-making processes is an action-oriented process involving those affected by institutions and initiatives, and affording them control over decisions that affect their lives. This paper focuses on participation in policy-making processes by persons with epilepsy during the development of the Intersectoral Global Action Plan on Epilepsy and Neurological Disorder (IGAP) by WHO. Person(s) with lived experience (PWLE) are regarded as '*experts by experience'* in the scope of their first-hand experience with a diagnosis or health condition. Research suggests that including PWLE in policy development significant significantly contributes to building trust and overall outcomes. This paper describes the inclusion of the author and two other persons with epilepsy from Africa in the development of IGAP.
Method: This paper describes the inclusion of a PWLE on our research team. I provide a review of the engagement processes that were used during the development of IGAP and how persons with epilepsy were involved. I used autoethnography as a lived experience researcher based on my personal experience to describe and critique practices of participatory approaches used in the development of IGAP. I also acknowledged and valued my relationships with others with epilepsy and I include a narrative note from other two persons with epilepsy, who also contributed significantly to the development of this paper.
Results: PWLE participation fostered transferrable non-cognitive skills and competencies. Connecting with peers through active engagement allowed PWLE to build social capital, an important competency for joint actions which allowed achieving objectives usually beyond a single individual's reach. PWLE felt that their views and needs were being included and respected developing a positive sense of self-awareness and identity, which in turn increases resilience and well-being
Conclusion: Including PWLE in active roles in policy-making can benefit them in skills development, and self-perception as valued partners.

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Transitioning from paediatric to adult care in epilepsy: lived experiences

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Purpose: Transition into adulthood and adult medical care is an important step in the life of young people with epilepsy.
We aimed to gain a better insight in the lived experience of transitional medical care in epilepsy to improve future transitional care.
Method: This was a cross sectional observational study. We used digital focus group meetings and interviews with young persons (n=17) with all types of epilepsy, or their primary caregivers (n=20) if they had intellectual disability (ID). Participants came from two centres in Sweden. The participants included young people and caregivers before and after transition to adult medical care. We used thematic analysis to analyse the data from the focus groups and

interviews.
Results: Analysis revealed that participants before transition to adult medical care experienced transition as a non-issue: they had no clear expectations and they did not perceive that they had received information from supporting health professionals or were not involved in planning. Participants after transition experienced the transition as an unstructured process they felt unprepared for. Themes after transition included: uncertainty about the timeline, uncertainty about availability of the medical staff during the transfer process, and unmet needs regarding mental health and neurodevelopmental difficulties. Further themes for the group without ID after transition were impact of epilepsy on career decisions, the need to consider other co-morbidities and other transitions (school, leaving parental home, other medical care), driving regulations and own identity. Themes for the caregivers of participants with ID included barriers and anxiety regarding meeting new health professionals with limited knowledge of their child and their condition and difficulties navigating the healthcare and social service systems and community-based support systems.
Conclusion: Transitional care for adolescents with epilepsy in Sweden is experienced as an unplanned event with many unmet medical, psychological and social needs.

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Study of perceptions, attitudes and knowledge of nurses about epilepsy in Asian community

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Purpose: To assess knowledge, perception and attitudes of nurse in care of epilepsy-patients.
Method: From October 2016 : Questionnaires based study consisted of two sections. 1] Information about
neurological disorder like epilepsy 2] Methods to elicit nurses' knowledge perception and attitudes in care of epilepsy patients.

All questionnaires were returned and analyzed using simple statistical method. We also designed framework for orientation/CME that would novices to experts in providing nursing care for epilepsy patients. This presentation outlines role of nurses, impact on patient outcomes and education required for competent practice.
Results: N=31 nurses aged between 20-35 years enrolled from District hospital & rural catholic mission in rural/tribal india . 21 females, 10 males. knowledge, perception and attitudes of nurses towards epilepsy care is minimal with only 10 showing special skill, perception and good attitudes towards caring for epilepsy patients as opposed to 9 with little knowledge and low perception to caring for epilepsy patients and the remaining 4 with no specific knowledge and perception towards nursing care of epilepsy patients.
Conclusion: nursing is an important specialty but neglected in rural asia. Resources are scarce for such initiatives. Trained nurses can improve QOL of epilepsy patients. This presentation

will highlights role of cancer-nurses, impact on patient QOL, and education required for competent clinical care of epilepsy patients.

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A professional women's perspective of working in the epilepsy field

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Purpose: Sex and gender disparities remains a problem that impacts professional experience of medical professionals identifying themselves as women across all medical fields. The scope of this disparity in the field of epilepsy remains unaddressed. Our study aimed to collect the opinions and lived experiences of women working in the fields related to epilepsy worldwide to summarize for the first time the sex/gender-related problems they face.
Method: We conducted a global cross-sectional survey investigating the personal experiences of women working in the epilepsy field. Surveys were available in English, French, and Spanish.170 responses were analyzed.
Results: The mean age of the participants was 40.5 years(IQR=46.5-32), and they resided in 30 different countries. 99%(n=82) identified as female. When asked if they feel the need to work harder than male colleagues to be respected or treated equally, 56.6%(n=83) said "yes" and 76.3%(n=59) recounted they had experienced Imposter Syndrome. 32.9%(n=85) stated they had experienced gender-based discrimination at their workplace. For those who were parents, 68.3%(n=41) reported feeling that their academic/clinical role had been impacted by having children. 58.8%(n=85) answered "yes" when questioned if they think men earn more than women do in a similar professional role as themselves. 67% of participants stated they were leaders in a workplace project and 58.8% of all participants felt overwhelmed by their professional duties often enough that the stress affected their daily lives. 45.2% of participants reported having a woman mentor and 38.8% had a woman supervisor/chair. When asked if they felt safe confiding in men colleagues/supervisors regarding workplace issues, 53%(n=83) said "yes", and 37.3% said "sometimes".
Conclusion: This is the first study investigating the impact of gender disparities in the epilepsy workplace. These preliminary results suggest that professional women are subjects to sex-related disparities, and this study opens the conversation for new opportunities and changes in the workplace environment.

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A review of documented driving discussion during clinical encounters in patients with epilepsy

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Purpose: Understanding and implementation of driving guidelines plays an integral role is managing patients with epilepsy. Epilepsy is a well established risk of road traffic accidents. In Ireland, as per the Medical Fitness to Drive Guidelines (April 2022), patients must be seizure free for one year from the date of last seizure. In our institution, St Jame's Hospital, our standard of care includes documentation of driving status at every clinical encounter. The following service evaluation aims to review this rate of documentation in our outpatient's clinic.
Method: We retrospectively reviewed consecutive attendance to our outpatients department (St. James's Hospital Dublin) from Jan 3rd to Jan 25th, 2023. Our clinic includes both virtual and face-face appointments. Clinic notes were examined with the search terms; "driver", "car", and "vehicle".
Results: We identified 66 clinic attendees of which 59 patients (mean age 39y) were included. 6 were excluded due to either presenting with a diagnosis other than epilepsy, or the documentation not yet available. Driving discussion was not documented in 54% (n=32) of clinical encounters. Driving status was therefore not known in 44% (n=26) of patients. Among patients with a documented driving status (n=33), 45% (n=15) were drivers and 55% (n=18) did not drive. At least 61% (n=36) of patients were not legally entitled to drive based on their reported seizure frequency, with 25% (n=9) of these patients not having documentation to confirm they were informed of this restriction.
Conclusion: Educating patients with epilepsy on driving guidelines and potentially informing patients of necessary driving restriction is an essential aspect of epilepsy management. In our department, in accordance with international guidelines, we strive to discuss driving in every clinical encounter. Current evidence suggests this is not being reached. Education among clinical staff and patients alike on driving restriction is crucial to maintaining safe epilepsy management.

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Employment outcomes after epilepsy surgery

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Purpose: Patients submitted to epilepsy surgery can achieve a better quality of life not only because of improved seizure control, but also due to employment gains and social adjustment. Previous studies showed that younger age at surgery, higher level of education and good prognosis after surgery are associated with employability. We aim to analyze employment outcomes in patients with focal epilepsy submitted to ressective surgery.
Method: Retrospective study of patients consecutively submitted to ressective surgery in a

Portuguese Refractory Epilepsy Center, between 2011-2021. A telephone survey was used to assess demographic characteristics and employment status before and after surgery.
Results: Out of 76, 55 patients were included, with median age at surgery of 40 years and current median age of 46. Median follow-up was 7.3 years (IQR 5.6-9.2). Level of education was primary school in 14.8%, 64.8% secondary school and 20.4% at least bachelor's degree. Prior to surgery, 90.9% of patients were employed, decreasing to 76.4% after surgery. Duration of epilepsy, age at surgery, level of education and seizure freedom status didn't influence employment status after surgery. Factors related with non-employed status were maintenance of seizures (n=5), unemployment by termination of contract or dismissal (n=2), early retirement in patients with surgery performed >50 years of age (n=3) and development of psychotic condition after surgery (n=1).
Conclusion: In our population and despite seizure control, as opposed to previously published studies, epilepsy surgery didn't have a positive impact on employment outcomes. Small sample size might have influenced our results and further studies regarding social adjustments and other factors influencing employment issues should be pursued in the future.

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A retrospective cohort study on the management of early and established status epilepticus

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Purpose: To investigate the management of early and established status epilepticus (SE) including timing, dosing and selection of benzodiazepines and second line treatments.
Method: Single-centre, retrospective observational cohort study. Data was collected on first-, second- and third-line treatment and outcomes.
Results: 252 cases were studied. Seizures terminated spontaneously in 54% cases. 116 (46%) cases were given benzodiazepines, of which 29 (25%) were given at least one benzodiazepine by family/carers, and 72 (62.1%) received benzodiazepines by ambulance services. Benzodiazepines terminated seizures in 71.6% cases. The commonest benzodiazepine was buccal midazolam (35.5%). Median time to first benzodiazepine was 14.5 (6-27) minutes. We found a positive correlation between time to first benzodiazepine and time to seizure cessation, progression to second- and third-line treatment, and occurrence of respiratory complications ($p<0.05$). 73/116 (62.9%) received a correct dose of benzodiazepine. Underdosing was most common, and was associated with longer seizure duration and progression to second-line treatment ($p<0.05$). 33/116 (28.4%) cases progressed to second-line treatment, and the mean time to second-line treatment was 59.4 minutes (±32.3 minutes). The commonest second-line ASM was Levetiracetam (53.8%), followed by Phenytoin (43.6%). Second-line treatment terminated seizures in 57.5% cases. 14/116 (12%) cases progressed to third-line

treatment; mean time to treatment was 60.6 minutes (±22.24 minutes). Anaesthetic agents included propofol and fentanyl. Respiratory complications occurred in 6.75% cases; none were due to benzodiazepines. There were two deaths in refractory SE, both had pre-existing end-stage brain malignancies.
Conclusion: These data confirm that delays in benzodiazepine administration, incorrect dosing and suboptimal benzodiazepine selection contribute to longer seizure duration, increased likelihood of progression to second- and third-line treatment and occurrence of respiratory complications. Efforts to increase awareness of status epilepticus as a time-sensitive emergency with high mortality and morbidity are needed.

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STEPPER (Status Epilepticus in Emilia Romagna): therapeutic interventions and quality of care in Emilia-Romagna Region, Italy

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Purpose: SE (status epilepticus) is one of the primary neurological emergencies. Several studies conducted in Emilia Romagna Region (ERR) northern Italy, in the previous two decades have shown that mortality is still high and variable in different areas: 39% Bologna, 31.5% Modena, 50% Parma. STEPPER(STatus EPilePticus in ER – STEPPER- RF-2016-02361365) aimed at studying clinical characteristics, management and prognostic factors of SE in the adult population of the ERR, with particular focus on refractory SE (RSE) and non-convulsive SE (NCSE).
Method: We conducted a multicenter prospective observational study on adult patients with SE in 17 neurological and intensive care units in ERR between October 2019 and October 2021. Follow-up was performed thirty days after SE onset.
Results: 610 cases were recruited: 56% female; mean age 70 years; 54% with prominent motor symptoms; 46% NCSE of which 30% in coma. 32.5% of patients had a previous diagnosis of epilepsy. 43% of patients had an in-hospital onset of SE. Etiology was known in 87% of SEs (acute 49%, remote 27%, progressive 20%, definite epileptic syndrome 3%). The mean pre-SE Rankin score was 2; mean STESS and EMSE were 3 and 71, respectively. 34% of cases were RSE. Benzodiazepines were used well beyond the first line of treatment, while only 47% of RSE cases received a third-line therapy with anesthetic drugs. Thirty-day mortality was 24% in the whole population, 24% in NCSE, and 38% in RSE. The mean Rankin score at 30 days

follow-up was 3.
Conclusion: This prospective multicentric study confirmed high 30-day mortality of SE and a worsening of functional outcome in survivors. High EMSE scores are in line with a poor prognosis in our cohort. Poor adherence to SE treatment guidelines might have influenced the prognosis in some cases.

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Developing the methodological foundation for NORSE surveillance

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Purpose: New-onset refractory status epilepticus (NORSE) is associated with high mortality and morbidity but remains poorly understood. We sought to develop an EMR-based case definition to inform future population-based surveillance.
Method: Our study included any patient admitted to a Mount Sinai Health System (MSHS) ICU (excluding Neonatal) in 2019. A data collection form was developed, tested and used by trained reviewers. Every admission in a randomly selected month was reviewed to determine if they were coded for seizure. We then reviewed all charts with an ICD-CM diagnosis code for seizure/epilepsy. NORSE cases were confirmed by two epileptologists. Chart review data were linked to MSHS EMR data. We built algorithms with diagnosis codes, anti-seizure, immunomodulatory or anti-microbial medications, procedures and length-of-stay. We calculated sensitivity (Sn) specificity (Sp), negative (NPV) and positive predictive value (PPV) with 95% confidence intervals and Youden's Index of each case definitions.
Results: There were 13,694 ICU admissions. 1851 charts were reviewed. We identified 173 admissions with definite status epilepticus and 3 with definite NORSE. The 5 best performing algorithms were: ICD for status epilepticus + ≥2 antiseizure medications (ASM) (Sn 1, Sp 0.916, PPV 0.019, NPV 1); ICD for status epilepticus + ≥2 ASM + brain biopsy (Sn 1, Sp 0.995, PPV 0.25, NPV 1); ICD for status epilepticus + ≥2 ASM + text containing "epilepticus" or "NORSE" (Sn 1, Sp 0.926, PPV 0.029, NPV 1); ICD for status epilepticus + ≥2 ASM + length-of-stay ≥14 days (Sn 1, Sp 0.957, PPV 0.036, NPV 1); ICD for status epilepticus + length-of-stay ≥14 days (Sn 1, Sp 0.946, PPV 0.029, NPV 1).
Conclusion: NORSE remains a rare neurologic disorder but can be identified using case definitions that are both sensitive and specific. Future work will validate these definitions in other healthcare systems.

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Super-refractory status epilepticus: a systematic review and meta-analysis of outcomes and treatment approaches

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Purpose: Super-refractory status epilepticus (SRSE) is defined as status epilepticus (SE) not responding to third-line treatment with sedation. Current clinical knowledge of the disease and optimal treatment approach is sparse. The study aimed to systematically assess outcomes at discharge and treatment approaches for patients with SRSE.
Method: We performed a systematic literature search in MEDLINE, Cochrane Library, EMBASE and clinicaltrials.org up to May 5th 2022. Studies including adult patients (≥18 years of age) with SRSE were considered for inclusion. Animal studies, review articles, and studies with inadequate patient description were excluded.
Results: 94 articles and 30 conference abstracts were included reporting 1180 patients with SRSE. Data from 266 individual patients with an average duration of SRSE was 36.3 days, a mean age of 40.8 years, and equal sex distribution were available for meta-analysis. SRSE had a distinct pattern of etiologies with acute cerebral events and unknown accounting for 41.6% and 22.3% of all etiologies. Reports on SRSE caused by e.g., alcohol, drugs or tumors were rare. Established prognostic factors like age and etiology were not associated with outcome. At discharge, 73.6% had died or were moderately-serverely disabled (in-hospital mortality: 24.1%). Reported treatment with ketamine, phenobarbital, other barbiturates, vagus nerve stimulator and ketogenic diet was not associated with outcome.
Conclusion: SRSE patients are distinct due to the pattern of care (e.g., long-term treatment to younger patients without negative prognostic factors and unknown/non-malignant etiologies) and the natural course of SE. Long-term treatment was associated with high odds of cessation of SRSE but increased risk of disability.

The study was funded by a scholarship from the University of Southern Denmark to CDC and the free research grant from the Region of Southern Denmark to CPB.

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Cerebral glucose metabolism in possible non-convulsive status epilepticus with lateralized periodic discharges

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Purpose: This study aimed to investigate the association between lateralized periodic discharges (LPDs) and hypermetabolism on ^{18}F-fluorodeoxyglucose (FDG)-PET in patients with possible non-convulsive status epilepticus (NCSE). In the current recommendation, possible NCSE should only be considered when LPDs fulfill the criteria of the ictal-interictal continuum (IIC). FDG-PET hypermetabolism is a potential useful biomarker to label these patterns as

ictal.
Method: Patients with possible NCSE and LPDs on EEG who underwent FDG-PET were retrospectively and prospectively included. Two blinded neurologists independently interpreted the EEGs, and a blinded nuclear medicine specialist evaluated the FDG-PET images for focal hypermetabolism, including semiquantitative analysis of the maximal standardised uptake value (SUVmax) relative to the SUVmax of the pons (SUVr pons). The correlation between EEG characteristics and SUVr pons was studied.
Results: Eighteen patients were included (12 women and 6 men). Median age was 62 years (range: 23-84). Median frequency of LPDs was 1 Hz (range: <0.5-2.5). Plus factors were present in 10 (56%). Prevalence of LPDs was continuous in 7 (39%), abundant in 6 (33%), frequent in 4 (22%) and occasional in 1 (6%). Evolution was present in 3 (17%), fluctuation in 7 (39%), and LPDs were static in 8 (44%). Fourteen EEGs (78%) fulfilled the criteria of IIC. Fifteen patients (83%) had focal hypermetabolism on the side of the LPDs. A strong positive correlation was found only between the prevalence of LPDs and SUVr pons (Pearson's $r = 0.54$, $p = 0.02$; linear regression: correlation coefficient = 1.03, $R^2 = 0.29$, $p = 0.02$).
Conclusion: FDG-PET hypermetabolism is common in possible NCSE with LPDs. The main determinant was LPD prevalence. Hypermetabolism was found in three patients (17%) with EEG patterns that did not fulfill IIC criteria. We suggest that functional imaging, such as FDG-PET, should have its place in the diagnostic work-up of possible NCSE.

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Predictors and outcome of nonconvulsive status epilepticus in patients after cardiac surgery

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Purpose: In the cardiac surgical population, the true incidence of nonconvuslive status epilepticus (NCSE) and its impact on outcome is still unknown. The aim of this retrospective study was to evaluate the frequency of NCSE after adult cardiac surgery on cardiopulmonary bypass (CPB) and to describe specific characteristics and clinical outcome of affected patients.
Method: All patients who underwent heart operations with CPB between January 1, 2014 and June 30, 2015 have been screened for allocations to the Department of Neurology and a subsequent EEG examination The recently validated Salzburg criteria have been applied for the diagnosis of status epilepticus. All patient demographics, their past medical and neurological history as well as perioperative data were collected retrospectively.
Results: Within 18 months, 1457 patients had cardiac surgery on CPB. EEG was requested

for 89 patients. Seizures were detected in 39 patients and NCSE was detected in 11 patients. Open heart surgery was performed in all 11 NSCE patients, of whom eight showed concomitant brain insults. None had a history of epilepsy. Despite the inhibition of seizure activity with antiseizure medication, clinical improvement was only noted in seven NCSE patients, three of whom were in cerebral performance category 2 and four in category 3 at hospital discharge. The four patients without neurological benefit subsequently died in the ICU.
Conclusion: The occurrence of NCSE after open cardiac surgery is significant and frequently associated with brain injury. In this study, neurological complications potentially associated with seizure activity after cardiac surgery on CPB were also related with re-operative surgery, urgent and open-chamber procedures, renal insufficiency, cerebrovascular disease, aortic atherosclerosis, cardiopulmonary resuscitation and a prolonged duration of anesthesia causing tremendously increased morbidity and mortality. It seems prudent to perform EEG studies early to interrupt seizure activity and mitigate secondary cerebral injury.

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Pharmacokinetic, pharmacodynamic, and safety study of intravenous ganaxolone in healthy adult volunteers

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Purpose: Ganaxolone, a neuroactive steroid anticonvulsant, rapidly alters neuronal excitability by modulating both synaptic and extrasynaptic γ-aminobutyric acid ($GABA_A$) receptors. The objective of this study was to assess the pharmacokinetics (PK), pharmacodynamics (PD) and safety of IV ganaxolone.
Method: A phase 1 clinical trial of IV ganaxolone in healthy subjects. In Stage 1, subjects received either vehicle control (n=6) or IV ganaxolone administered as a 5-minute bolus of 10mg (n=3) or 30mg (n=3); a 2-minute bolus of 20mg; or a 60-minute infusion of 10mg (n=6) or 30mg (n=6). For Stage 2, IV ganaxolone was administered as a 6mg bolus over 5 minutes followed by a continuous infusion of 20mg/hour over 4 hours (n=6). PK was evaluated by non-compartmental analysis and multiple PD assessments, including bispectral index (BIS), and safety data were collected.
Results: 36 subjects were enrolled. PK values varied between cohorts and corresponded to the dose and rate of administration. After administration of IV ganaxolone over 2, 5, or 60 minutes, time to maximal BIS reduction was a median (range) of 8 minutes (5, 15), 15 minutes (5, 60), and 65 minutes (30, 120), respectively. In Stage 2, time to maximal BIS reduction was 148 minutes (35, 220). Deep sedation was reported in a single patient 5 minutes post-administration of a 30mg IV bolus over 2 minutes with return to baseline arousal 15 minutes following administration. Rapid changes in qEEG parameters were more pronounced after administration of an IV bolus over 2 or 5 minutes. No deaths, severe adverse events (AEs), or serious AEs (SAEs) were reported.

Conclusion: After administration of IV ganaxolone, a dose and administration duration-dependent effect on PK and PD was observed. More pronounced and rapid effects occurred in subjects receiving ganaxolone IV bolus over 2 or 5 minutes. IV ganaxolone was generally well-tolerated at the doses studied.

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Effect of trans 4-butylcyclohexane carboxylic acid (4-BCCA) upon epileptogenesis and neurodegenerative changes following status epilepticus

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Purpose: 4-BCCA, a low-affinity inhibitor of AMPA receptors at the trans-membrane domain have been suggested as potential new treatment for epilepsy control but its potential disease-modifying effects in SE and neurodegeneration have not been investigated.
Method: We investigated the effect of 4-BCCA along with standard ASDs [valproate (VPA) and perampanel (PER)] in Li-pilocarpine induced status epilepticus rat model. Optimal dose finding study of 4-BCCA was performed considering 80 to 200mg/kg doses of 4-BCCA followed by acute and long term effect study. Assessment of neurobehaviour (by elevated plus maze and passive avoidance), neurodegeneration [by transmission electron microscopy (TEM) and immunohistochemistry in hippocampal slices], total antioxidant capacity (TAC) and neuronal loss [by neuron specific enolase (NSE) in cererbral tissue] were performed.
Results: 4-BCCA at 200 mg/kg. i.p. was found to be optimal and in comparison to other ASDs it showed better seizure control in terms of latency and number of stage 3/4 seizures. PER group and 4-BCCA+PER showed better memory retention but without significant difference among the drug-treated groups. In TEM, 4-BCCA+PER and 4-BCCA+VPA group showed less nucleus and cytoplasmic changes. In immunohistochemistry 4-BCCA, PER and combination groups showed better neuronal viability. 4-BCCA+ PER showed higher TAC and lower NSE level.
Conclusion: 4-BCCA alone and its combination with ASDs especially perampanel in status epilepticus model in rats showed better seizure control and neuroprotection.

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Machine learning applications to differentiate focal epilepsy from generalized epilepsy

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adelphia, United States, [3]Shiraz University, Shiraz, Iran, Islamic Republic of

Purpose: To evaluate the feasibility of utilizing clinical information of patients with epilepsy (PWE) to differentiate focal epilepsy from idiopathic generalized epilepsy (IGE) by application of machine learning methods.
Method: This study used a large database of PWE that was built over 14 years. All patients with a diagnosis of focal epilepsy or IGE (two major epilepsy types in adolescents and adults) with an age at seizure onset of 10 years or older were studied at the epilepsy center at Shiraz University of Medical Sciences, Iran, from 2008 until 2022. The senior epileptologist suggested nine easily obtainable clinical features (based on a detailed history and physical examination) including age at seizure onset, sex, a history of febrile convulsion, a family history of epilepsy, a history of severe head injury, a history of medical comorbidity, aura with seizures, ictal-related tongue biting, and abnormal physical examination to be utilized for the classification. The dataset was divided into train (70%) and test (30%) subsets, using the stratified random portioning method. The classification framework benefited from multiple classifiers including Support Vector Machine, Logistic Regression, K-Nearest Neighbors, Random Forest, Gradient Boosting, Adaptive Boosting, Bagging, and Extremely Randomized Trees. Their results were given to a Stacking classifier as an ensemble method to perform the final classification using the best results. Hyper-parameters were trained using grid search and validated on 5-fold cross-validation.
Results: 1445 patients (964 with focal epilepsy and 481 with IGE) were available for the experiment. The classification results of test data demonstrated 0.81 precision, 0.81 sensitivity, 0.77 specificity, and 0.81 F1-score.
Conclusion: Machine learning applications may help differentiate focal epilepsy from IGE using easily obtainable clinical features. Such applications would be very helpful to correctly differentiate common epilepsy types from one another (focal vs. IGE) in places with a lack of experienced medical professionals.

Digital Poster Presentations

Adult Epileptology

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Compliance, side effects, and psychosocial outcomces in adult epilepsy care in western Sweden: initial report from the region-wide PREDICT study

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Purpose: Studies of realworld adult epilepsy care are often single-center, register-based, or predate the era of new ASMs. Prescription data studies show high retention rates of the first ASM in Sweden, but cannot provide further detail. The PREDICT (Prospective Regional Epilepsy Database and biobank study for Individualized Clinical Treatment) is a longitudinal study at the five largest public epilepsy care providers in western Sweden. Aims include finding risk factors of poor adherence to treatment, side effects, and negative psychosocial outcomes.
Method: PREDICT (clinicaltrials.org:NCT04559919) is a regional prospective study of epilepsy in Region Västra Götaland (population 1.7 m). Adults with first seizures or epilepsy are recruited at five epilepsy care providers, including the regional tertiary epilepsy center. After informed consent, epilepsy characteristics are extracted from the medical records and participants anwer a survey including seizure situation, compliance, and side effects. Patients are followed prospectively in medical records, national registers, and repeat surveys.
Results: By December 2022, 433 patients had been recruited. Compared to register data the cohort was representative regarding age (mean age 46) and sex (48.6% male) of patients seen by neurologists in VGR. The marjority (60.5%) had focal epilepsy. Forty-one percent reported side effects of their current ASM regime, 50.1% had forgoten to take their ASM in the last year, and 33% had forgotten to do so multiple times. Side effects were more common among those stating non-adherence. Nearly 60% were currently employed.
Conclusion: We found high rates of non-adherence and side effects, which could reflect less-than-optimal follow-up in standard epilepsy care. Analyses of risk factors of non-adherence and relationship to the seizure situation are ongoing. The PREDICT study will hopefully provide insights on which patient groups need particular attention from health services for optimal epilepsy outcomes and illustrates the need for observational studies using primary sources, as a supplement to register-based investigations.

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Safety and tolerability of COVID-19 vaccines in people with epilepsy

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Purpose: The purpose of our study was to investigate the safety and tolerability of COVID-19 vaccines in people with epilepsy (PWE) and seizure control after vaccination.
Method: The study included 87 adult patients (>18 years of age) with epilepsy who received a full course of vaccination, including a booster dose of the vaccine. All patients were followed up for 6 months after receiving a booster dose of the vaccine. We collected patient data using a standard form. The form contained questions about patient demographics, current antiepileptic therapy, information about vaccinations, side effects and adverse events associated with epilepsy. Patients were divided into two groups: the first group included patients with an increase in the frequency of seizures, and the second group, patients with stable seizures. All patients were taking antiepileptic drugs.
Results: Of the 87 patients, 42 were male and 45 were female. In 83 patients (95.4%), there was no increase in the frequency of seizures, while in 4 patients (4.6%) there was an increase in seizures. Post-vaccination seizures occurred mainly within 7 days after the introduction of the vaccine. Patients in the first group were treated on average with more anticonvulsants and had a higher frequency of seizures before vaccination compared with patients in the second group, and it was patients in the first group who experienced an increase in seizures. There was no significant difference in the number of seizures before vaccination, month between doses, month after vaccination and within 6 months after receiving the booster dose in patients of the second group. None of the patients reported status epilepticus.
Conclusion: Our study shows that COVID-19 immunization is safe and welltolerated in PWE. The vaccines had no effect on the monthly number of seizures. Only a small number of patients experienceda short-term increase in the frequency of seizures.

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Presence of parkinsonism and limb dystonia in anti-Ma2-associated encephalitis: a case report, and review of the literature

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Purpose: We reported a 25-year-old man presented psychosis and memory impairment since the age of 21. Two years later, frequent right medial temporal lobe epilepsy developed, with the presence of transient conscious lapse and chewing. Additionally, episodic left-hand and foot dystonia occurred that were not related to seizure events. Physical examination revealed vertical gaze palsy and some parkinsonism features, like mask face and hypokinesia. The Tc-99m trodat image did not show the corresponding result. Magnetic resonance imaging (MRI)

showed bilateral hippocampal T2 hyperintensity and atrophy. 18-FDG- PET disclosed relatively symmetrical uptake in the basal ganglia (BG), thalamus, and cerebellum, with bilateral hippocampal hypermetabolism. The electroencephalogram presented abundant and transient periodic sharp waves at F8-T2 and alternating temporal intermittent rhythmic delta activities. Anti-Ma2 antibodies were finally identified from his serum. There was no positive finding after whole-body tumor screening. Dystonia only partially improved after a low-dose trial of levodopa, but moderately improved after plasmapheresis. Based on this phenomenon, we hypothesized that the asymmetrical involvement of the deep gray matter occurred in anti-Ma2-associated encephalitis.
Method: We conducted electronic searches in the PUBMED, EMBASE, ScienceDirect with keywords of ('anti-ma2-associated encephalitis' OR 'anti-ma2 antibody' OR 'anti-ma2 receptor') AND ('movement disorders' OR 'hyperkinetic' OR 'hypokinetic' OR 'dyskinesia' OR 'dystonia' OR 'chorea').
Results: Anti-Ma2-associated encephalitis comprised a spectrum of limbic, diencephalic, and brainstem syndromes. Atypical parkinsonism accounts for around 10% of the patients. Movement disorders such as chorea and dystonia were rarely reported. Dopamine transporter and metabolic images could not well demonstrate the corresponding basal ganglion lesion. BG and brainstem involvement in anti-Ma2-encephalitis had been reported. Nonetheless, which structure involvement is related to dystonia and parkinsonism in anti-Ma2 antibodies has not been concluded.
Conclusion: Future research for the mechanism of the asymmetrical limb dystonia in anti-Ma2-associated encephalitis is warranted.

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Comparison of valproate use in male versus female patients with juvenile myoclonic epilepsy treated at a complex epilepsy centre

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Purpose: Juvenile myoclonic epilepsy (JME) is a subtype of idiopathic generalised epilepsy (IGE) affecting 5-11% of patients with epilepsy. Valproate is an effective anti-seizure medication (ASM) for this syndrome. However there are significant challenges prescribing valproate due to teratogenicity. We aim to study factors associated with drug-refractory (failed ≥2 ASMs) JME and the use of valproate in males versus females.
Method: We performed a retrospective study of consecutive patients with JME treated at Beaumont Hospital extracted from our epilepsy Electronic Patient Records (EPR). We included patients aged between 18 and 55, with an abnormal EEG compatible with JME/IGE, history of myoclonus, and under active follow up. Baseline clinical data was obtained from EPR. Statistical analyses were completed using STATA, significance level was set at $p<0.05$, and Fisher's exact test for analysis between groups.

Results: We included 100 patients; eighty-three were female. Mean age of the cohort was 33.9 years. 36 patients (36%) met the criteria for drug-refractory epilepsy; 35 were female. All patients had myoclonus, 93% had generalised tonic-clonic seizures, and 52% had absences. Median of current ASM was 2 (range 1-5). Median of failed ASM was 2 (range 0-13). Valproate is currently prescribed in 21% of patients (12 males: 9 females). Of the female patients currently prescribed valproate the median of failed ASMs was 4 (range 1-8). In men prescribed valproate the median number of failed ASMs was 1.5 (range 0-3). Female gender was a statistically significant (p= 0.0045) risk factor associated with refractory JME. Valproate use in females was more likely in those with refractory JME (p=0.0464). Psychiatric co-morbidity associated with refractory JME was also statistically significant (p= 0.0357).
Conclusion: JME incidence is higher in women and female patients are more likely to become drug-refractory. Valproate is used cautiously in our centre but still has value in females with drug-refractory JME.

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How does a three-month ketogenic diet affect the hormonal profile? a pilot study in adults with pharmacoresistant epilepsy

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Purpose: Epileptic seizures seem to be affected by hormonal fluctuations in both sexes: high testosterone levels may impact seizure control, while elevations in estradiol appear to lower the seizure threshold. The ketogenic diet (KD) is a therapeutic alternative for patients with pharmacoresistant epilepsy. The modified Atkins diet (MAD) is a KD protocol with less food restriction, higher tolerability, and palatability.
Method: To evaluate the effect of MAD on hormonal oscillations, we enrolled 21 patients with epilepsy (PWE) and followed up for three months. Progesterone, testosterone, estradiol, cortisol, prolactin, thyroid-stimulating hormone (TSH), and luteinizing hormone (LH) were assessed at the pre-diet period (baseline) after four and 12 weeks of dietary treatment. In addition, adverse effects associated with MAD and seizure frequency were evaluated. There were four losses of follow-up and six refusals to follow the protocol.
Results: A significant reduction in seizure frequency ($p<0.001$) was observed in both sexes (4 women; mean age = 33.7±8.96 years; 7 men; mean age = 31.3±9.10 years). There was a significant reduction in FSH ($p=0.006$), progesterone ($p<0.001$), and estradiol ($p <0.001$) from the pre-diet period to 12 weeks and in LH ($p<0.001$) from 4 to 12 weeks in women. A significant increase in cortisol ($p<0.001$) from 4 to 12 weeks and in testosterone ($p<0.001$) from baseline to 4 weeks and from 4 weeks to 12 weeks in women was also noticed. Men had decreased prolactin levels ($p=0.041$) from baseline to 4 weeks and a significantly reduced TSH ($p<0.001$) from the pre-diet period to 4 and 12 weeks.
Conclusion: KD was effective, considering the patients achieved a minimum of 50% reduction

in seizure frequency. There is scarce literature on hormonal variations associated with KD. Despite the aspects that lead to hormone oscillation (sex, pharmacotherapy, age), KD seems to contribute to these hormonal oscillations parallel to seizure control.

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Risk of epilepsy and status epilepticus occurrence in post carbon monoxide poisoned patients: aationwide population-based cohort study

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Purpose: To investigate association between carbon monoxide poisoning and risk of epilepsy and status epilepticus.
Method: This nationwide population-based cohort study was conducted by using the administrative database of the National Health Insurance Service of Korea. Individuals aged ≥18 years with ICD-10 code of T58 as a principal or adjuvant diagnosis between 2002 and 2021, were defined as acute CO poisoning group. A total of 53,380 patients with CO poisoning and 53,380 controls matched for age, sex, insurance type, income level, and region of residence were included in this study. Incidence rates for outcomes, and hazard ratios (HRs) for CO poisoning group over the study period was analyzed. Multiple multivariable models were generated with the following covariates: birth year, sex, index date, insurance type, income level, location of residence, Charlson comorbidity index, central nervous infection, and Parkinson disease at the index date diagnosed based on ICD-10 code. Furthermore, risk for developing epilepsy and status epilepticus with CO poisoning were compared between patients who had hyperbaric oxygen therapy at the acute poisoning and those who had not.
Results: Mean age of participants at index year was 45.7 ± 17.1 in both groups. Cumulative incidence of epilepsy and status epilepticus were persistently higher during the whole observation period in the CO poisoning group. The overall risk of epilepsy was increased in CO poisoning group (HR 2.60; 95% CI, 2.43-2.78). Overall risk of status epilepticus was increased in CO poisoning group (HR 4.10; 95% CI, 2.84-5.92). Among CO poisoning group, when estimated statistically from Model 3, hyperbaric oxygen therapy at the acute poisoning showed higher risk of epilepsy and status epilepticus than without (HR, 1.60; 95% CI, 1.47-1.75 and aHR, 1.75; 95% CI, 1.18-2.60, p<0.01).
Conclusion: CO poisoning and hyperbaric oxygen therapy is associated with increased risk of epilepsy and status epilepticus based on nationwide population-based cohort study.

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Visual hallucinations presenting as status epilepticus amauroticus

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Purpose: Visual hallucinations are commonly encountered by neurologists and non-neurologists on a daily basis. They however, are not thought of as seizures by most of physicians and therefore lead to a delay in diagnosis and treatment. Due to this, unnecessary treatment trials, consults to various specialties and admission to psychiatry units are not uncommon. This not only leads to iatrogenic side effects but also leads to increase in health care costs. We present such a case of new onset focal occipital seizures that led to status epilepticus amauroticus.
Method: Reviewed detailed medical history and physical examination along with diagnostic tests that include EEG, MRI of brain, and Lumbar puncture.
Results: Our 82-year-old adult reported persistent blind spot along with hemianopia that presented itself after a traumatic brain injury. He reported intermittent flashing lights in the center of his vision that were green, red, and orange in color lasting for seconds to hours over the past month. Baseline EEG captured 2 such episodes lasting for 1 minute each which were consistent with focal right occipital seizures. MRI of brain showed subtle leptomeningeal enhancement around the right medial occipital lobe. Two Lumber punctures performed 3 days apart failed to show any abnormality. Keppra resolved photopsias. Visual deficits also improved significantly with starting Keppra however, these took months for complete remission. Follow-up MRI and EEG demonstrated complete resolution of abnormalities.
Conclusion: Visual hallucinations are often neglected by Physicians as possible epileptic seizures. Visual epileptic seizures and status epilepticus amauroticus have been well defined in the literature but remain underdiagnosed or misdiagnosed due to lack of awareness. For such patients, there is substantial delay in treatment and often when trial basis treatments are started they lead to potentially severe iatrogenic side effects. Increase awareness is essential in timely mannered diagnosis and treatment is essential with visual epileptic seizures.

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International case control study of Sudden Unexpected Death in Epilepsy (SUDEP)

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Purpose: To identify factors associated with an increased or decreased risk of SUDEP.
Method: The EpiNet study group is undertaking a prospective case-control study of SUDEP. 200 people with epilepsy from pre-defined cohorts who die from definite or probable SUDEP will be included. For each case, three true controls and one proxy control are being recruited from the same cohort.
A structured telephone interview with the next-of-kin of SUDEP cases is conducted. Controls are asked about their epilepsy and lifestyle. Proxy controls are asked about the control patient they know. Information regarding seizure type and medication, sleeping arrangements, nocturnal supervision, use of seizure-detection devices, socio-economic factors and other health issues is entered into the EpiNet database. Pathologists' and coroners' data regarding circumstances and cause of death is recorded if available.
Investigators are paid a small sum to cover the actual costs of the study.
The data will be analysed to identify risk factors for SUDEP. Odds ratios will be calculated using the Mantel-Haenszel method and logistic regression to control for covariates. 200 cases and 800 controls will detect an odds ratio of 1.7 over a control exposure range of 22-65%, with 80% power and 95% confidence level (2-sided).
Results: 33 cases have so far been recruited from 6 countries in Asia-Oceania, Europe and North America. Approvals have been obtained for centres in another 10 countries. COVID-19 has adversely affected case enrolment, and new participants are welcome.
Conclusion: SUDEP is second only to stroke as the leading neurological cause of years of potential life lost. The causes remain uncertain. A large prospective case-control study is the best way to determine the extent of the association between specific variables and SUDEP, in particular, those that could be modified to prevent this tragedy. Anyone interested in participating is welcome to contact: epinetadmin@adhb.govt.nz.

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"All of a sudden I see myself – a microphenomenological analysis of out of body experiences in seizure descriptions"

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Purpose: Around 7% of people with seizures report Out of Body Experiences (OBEs) during epileptic seizures. Here we investigate in detail how OBE's unfold during epileptic seizures.
Method: Six people with focal seizures reported having OBEs, two were interviewed using the microphenomenological interview method, and four reported such experiences in conversations with their attending physician which were audio-recorded for research purposes. The recordings were transcribed verbatim and analysed following the microphenomenological analysis method, which allows a fine-grained analysis of the such experiences.
Results: We identified a clear temporal structure of seizures with OBE's consisting of five

distinct phases: 1) a premonition, 2) increasing pressure/nausea/upward tension 3) a bifurcation moment 4) either a strong or weak seizure 5) a recovery phase (long for strong seizures, short for less strong seizures). The OBEs occurred in Phase 1 for two participants, Phase 2 for two participants and in Phase 4 for three participants. Our analysis revealed two different types of OBE: one in which the person has the feeling that the perspective of their perception changes, and one in which the person sees themselves from the outside. The latter one was accompanied by fear, whereas the first one was neutral. The participants reported these phenomena late in the interaction with the physician or interviewer, indicating the difficulty in verbalising and sharing such experiences.
Conclusion: To the best of our knowledge this is the first microphenomenological analysis of OBEs in epileptic seizures. Our fine-grained analysis offers a valuable insight into these unusual experiences. We hypothesise that such phenomena are underreported and their prevalence underestimated.

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Memory and consciousness in focal seizures

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Purpose: Consciousness is defined as the ability to interact with the external world, subjective experiences and memory. The ILAE uses the term awareness as a marker of consciousness, assuming that patients who maintain awareness during seizure will be able to remember the event and report it. However, memory may be altered without affecting consciousness.
The objective of this work is characterize the memory in seizures and evaluate its relation with loss of consciousness (LOC).
Method: Consecutive patients of the videoEEG unit with focal epilepsy were included. Consciousness was evaluated by a third-person CSS scale (Artuis et.al), a first-person ICI (Cavanna. et.al) and SPS (Campora.et.al) to assess memory during seizure.
Results: We included 121 seizures from 79 patients. 46.3% did not remember anything, 38.58% remembered something and 14.9% remembered the entire event. Most seizures without remembers had profound LOC (74.1%), while in those who remembered everything did not have LOC (70.6%; p=0.0001, contingency coefficient 0.54, p=0.0001).
Seizures without memories had statistically lower ICI A than the events that remembered everything (3.75 ± 4.8 vs 8.2 ± 6.1, p=0.036). Memories were mainly of questions, orders or people who interacted. We found no difference in the ICI B values (without memory 1.47 ±

2.45 vs remember everything 2.2 ± 2.7, p=0.19).
Seizures with no recollection originated primarily in the temporal lobe (36/56), while those with full recollection originated in the frontal lobe (14/18, p=0.006).
Video review improved recall in 16.1% of cases, without statistical significance (p=0.6).
Conclusion: Memory can be affected independently of awareness. It is mainly affected when seizures had less awareness, assessed by the examiner (CSS) and by the patient (ICI A). Seizures from temporal lobe are the ones that most affect the memory of the episode. Characterizing the events that affect memory without altering awareness would help to better understand the functioning of the brain.

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Seizure remission following epilepsy surgery in a patient with late onset lesional Lennox-Gastaut syndrome: a case report

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Purpose: Background
Lennox-Gastaut Syndrome (LGS) is an epileptic encephalopathy with a peak age of onset at 3-5 years. It is characterized by multiple, generalized seizure types and an inter-ictal electroencephalogram (EEG) showing generalized slow spike-and-waves, generalized paroxysmal fast activity, and progressive cognitive regression. Late onset LGS is generally considered treatment resistant.
Method: Case
A 12-year old girl having an antecedent history of right focal clonic seizures associated with left frontal empyema at age 8-years for which she underwent surgical intervention was referred 18 months later, when she developed right focal clonic seizures, atonic and absence seizures.
Her inter-ictal EEG showed long runs of generalized high voltage spike-wave discharges at 1.5-2Hz and irregular persistent slow background. Video-EEG demonstrated generalized electro-decrement with or without brief runs of generalized alpha range activity with atonic seizures and generalized 1.5 to 2Hz spike wave runs with absences. A 3T MRI brain showed left middle frontal gyrus gliosis.
She underwent resection of gliotic tissue under electrocorticography, intra-operative neuro monitoring and mapping and MRI navigation.
At five months post-op, she remains seizure free. Although a generalized delta/theta range slowing persists, her EEG is free of epileptiform discharges.

Results: Resective surgery can be promising in LGS patients with localized seizure foci identified on EEG. Although, initial focal semiology supported seizure origin to be left frontal, our patient did not demonstrate focality on EEG during pre-surgical evaluation.
This case lends support to the concept of LGS phenotype as being a network epilepsy, where key cerebral networks become autonomously unstable and that cortical lesions are able to establish and maintain this abnormal unstable network behavior. Thus, resection of the lesional zone can abolish the focus of seizure genesis.
Conclusion: This case highlights the importance of considering lesionectomy even in late-onset-LGS despite
failure to demonstrate clinico-electro-anotomical concordance at a later point of evaluation.

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First year of experience of a newly established first seizure clinic

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Purpose: Early clinical and diagnostic assessment of a patient with new-onset epileptic manifestations is of crucial importance to define the underlying etiologies, guarantee a proper treatment and reduce the risk of seizure recurrence. In this study, we aim to show the data of the first year of “first seizure clinic” at our Epilepsy Center.
Method: We retrospectively reviewed the clinical, electroencephalographic and neuroimaging data of patients referred to the newly established “first seizure clinic” at the Regional Epilepsy Center of the Policlinico San Martino Hospital (Genova), from September 2021 to September 2022.
Results: Forty-five patients (median age 54.4 years, 60% men) were evaluated at our first seizure clinic. The diagnostic exams were all performed at the emergency department. A CT scan was performed in 39/45 patients, showing structural alterations in almost half of the cases, specifically a remote lesion in 18/22 and leukoraiosis in 4. Nineteen patients (42.2%) had already a diagnosis of epilepsy, while 26 patients (aged 59.7 ± 22.8 years, 53.8% men) presented with a first seizure. In the latter group, we observed EEG abnormalities in 13/26 (50%) of cases, either slow (9/13) or epileptiform waveforms (4/13). Twenty/twenty-six (76.9%) patients received a diagnosis of epilepsy and anti-seizure medication (ASM) was started. At the evaluation at the first seizure clinic, in five patients the hypothesis of an epileptic seizure was discarded. Also, in two patients the diagnosis of epilepsy was not confirmed and ASM was withdrawn.
Conclusion: Our data support the need for early epileptological evaluation in patients presenting with neurological manifestations suggestive of an epileptic seizure, as it is was revealed that this clinical suspicion was not confirmed in a significant number of cases, and treatment modified accordingly. Therefore, “first seizure clinics” may represent the standard

of care for the best and early taking charge of patients with new-onset epilepsy.

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Two sides to the one coin: stroke-like and seizure-like presentations of recurrent SMART syndrome

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Purpose: Stroke-Like Migraine Attacks after Radiation Therapy (SMART) syndrome is a rare, delayed complication of radiation therapy. Diagnostic criteria (Black 2006) include a remote history of cranial irradiation, prolonged reversible cortical signs and symptoms and transient diffuse unilateral cortical grey matter enhancement. Seizures and stroke-like episodes are recognised clinical features of SMART syndrome.
Method: We present the case of a 44-year-old gentleman with recurrent SMART syndrome presenting with two distinct clinical presentations: the first in which stroke-like events are prominent and a second presentation dominated by recurrent seizures.
Results: The first presentation was a marching cortical syndrome evolving over 2 weeks culminating in a right homonymous hemianopia, right-side spastic hemiparesis and sensory neglect. History was significant for a resected grade-3 oligodendroglioma in 2007, surgical revision in 2010 and post-operative radiotherapy. Focal epilepsy was previously well-controlled with anti-seizure medication. Admission Magnetic Resonance (MRI) demonstrated cortical hyperintensity and oedema in the previously irradiated brain with lepto-meningeal enhancement. The patient had one-isolated generalised tonic-clonic seizure. EEG captured no ictal activity.

A clinico-radiological diagnosis of SMART syndrome was made. Treatment was with steroids and anti-seizure medications. By month three the cortical-radiological picture had resolved and he was running 10 kilometers for leisure.

The second presentation occurred at month four. He re-presented with re-emergence of milder right-sided weakness. Focal motor and sensori-motor seizures were a prominent feature during this admission. Furthermore, recurrent electrographic seizure-activity was captured on EEG without clinical correlate. MRI brain was consistent with SMART syndrome. Steroids were re-introduced, anti-seizure medication was up-titrated and L-arginine was introduced.
Conclusion: Our case clearly describes two distinct clinical presentations of SMART syndrome in a single patient, highlighting the broad phenotype of this rare delayed complication of radiation therapy.

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Antiseizure medication withdrawal risk estimation and recommendations: a survey of American academy of neurology and EpiCARE members

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Purpose: Choosing candidates for antiseizure medication (ASM) withdrawal in well-controlled epilepsy is challenging. We evaluated 1) the correlation between neurologists' seizure risk estimation ("clinician predictions") versus calculated predictions, 2) how viewing calculated predictions influenced recommendations, and 3) barriers to using risk calculation.
Method: We asked US and European neurologists to predict two-year seizure risk after ASM withdrawal for hypothetical vignettes. We compared ASM withdrawal recommendations before versus after viewing calculated predictions, using generalized linear models.
Results: Three-hundred forty-six neurologists responded. There was moderate correlation between clinician and calculated predictions (Spearman coefficient 0.42). Clinician predictions varied widely, e.g., predictions ranged 5%-100% for a two-year seizure-free adult without epileptiform abnormalities. Mean clinician predictions exceeded calculated predictions for vignettes with epileptiform abnormalities (e.g., childhood absence epilepsy: clinician 65%, 95% confidence interval [CI] 57%-74%; calculated 46%) and surgical vignettes (e.g., focal cortical dysplasia six-months seizure-free mean clinician 56%, 95% CI 52%-60%; calculated 28%). Clinicians overestimated the influence of epileptiform EEG findings on withdrawal risk (26%, 95% CI 24%-28%) compared with calculators (14%, 95% 13%-14%). Viewing calculated predictions slightly reduced willingness to withdraw (-0.8/10 change, 95% CI -1.0 to -0.7), particularly for vignettes without epileptiform abnormalities. The greatest barrier to calculator use was doubting its accuracy (44%).
Conclusion: Clinicians overestimated the influence of abnormal EEGs particularly for low-risk patients and overestimated risk and the influence of seizure-free duration for surgical patients, compared with calculators. These data may question widespread ordering of EEGs or time-based seizure-free thresholds for surgical patients. Viewing calculated predictions reduced willingness to withdraw particularly without epileptiform abnormalities.

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Review of adult first seizure management in the district hospital

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Purpose: To assess first seizure management in adults at Basildon Hospital, acute general hospital, serving population of > 450,000.

Method: We retrospectively reviewed electronic medical records of patients ≥16 years of age seen at Emergency Department (ED) with first time in life seizures and reviewed in First Seizure Clinic (FSC). Patients admitted to Basildon hospital and seen by Neurologist in-patient were excluded from analysis.
Results: From 04/07/2021 to 11/01/2022, 384 adults with seizures were seen in ED, including 76 (19.8%) adults with first time in life seizures, discharged home and referred to FSC (75 referrals were sent the same or next day, one referral was missed). In cohort of referred to FSC, neurological status was recorded in 38 (50%) patients, ECG performed in 28 (36.9%) patients, safety measures and driving discussion recorded in 22 (28.9%) patients. In FSC, 64 patients (mean age 38,65 ± 18,29 years, 34 female, 30 male) were reviewed, data about 11 patients were not available, one appointment was not booked. The average time between ED referral and FSC review was 56.2 days (range from 0 to 140 days). After review at FSC, only 6 (9.4%) patients were diagnosed with epilepsy or epilepsy syndrome. More than one third of patients had seizure mimics, including syncope in 11 (17.2%) patients, acute symptomatic seizure in 7 (10.9%) patients (alcohol and recreational drug use, tumours and AVM, in one case seizure developed after Moderna COVID vaccination), psychogenic non-epileptic seizures (PNES) in 6 (9.4%) patients. Seven (10.9%) patients had previous seizures, highlighting the importance of obtaining relevant history at ED. Sixteen (25%) patients were still under Neurology investigation, 5 (7.8%) patients did not attend FSC appointment.
Conclusion: More ED teaching is needed on epilepsy diagnosis and management. The effect of first seizure proforma with 'prompts' of key actions for clerking doctors will be assessed by re-audit.

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Communication, communication, communication: experiences of navigating the first assessment of transient loss of consciousness

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Purpose: Transient loss of consciousness (TLoC) is one of the commonest neurological complaints. Over 90% is due to epilepsy, functional/dissociative seizures (FDS), or syncope. Missed/delayed diagnosis is common, affecting 20-30% of those with epilepsy or FDS. While developing a clinical decision aid for differential diagnosis of TLoC, we conducted a nested qualitative study to explore patient's experiences of assessment and management of TLoC.
Method: Semi-structured interviews with a purposive sample of adult patients (target *n*=30) with first presentation of TLoC. We transcribed and coded interviews and performed thematic analysis within a reflexive and contextualist framework. We present initial analysis of interviews conducted to date.
Results: Initial analysis identified three themes:

1. **(Dis)satisfaction with care received**: Participants were generally satisfied with the standard of care delivered; where dissatisfied, they attributed shortcomings largely

to lack of resources or staff workload, rather than individual failings.

2. **Understanding TLoC and its causes**: Participants mostly felt that they did not have a clear understanding of what had happened to them and did not receive adequate information to determine what caused their blackout.

3. **'No man's land'**: Participants described being left to await specialist assessment or results of investigations without understanding these next steps or how to self-manage in the interim.

Participants empowered with knowledge of investigation findings and able to assimilate them into understanding their TLoC were more satisfied and able to manage their symptoms and concerns, while those not provided with information in an intelligible format felt less able to continue with their lives.
Conclusion: TLoC represents a disorienting "biographical disruption" in a person's life. Even before a definitive diagnosis is reached, from first presentation communication (including differential diagnosis, significance of investigations and further assessments, and interim safety advice) is key to supporting ongoing self-management.

Work supported by NIHR grant 201992

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Seizure cycles under pharmacotherapy

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Purpose: In refractory focal epilepsy, cycles of epileptic brain activity influence seizures over multi-day (multidien) timescales, but the effect of treatment on these cycles and their link to seizure rates is unknown. We hypothesized that cycles of epileptic brain activity may decrease with successful pharmacological treatment.
Method: Interictal epileptiform activity (IEA) was recorded over years in 88 participants in the RNS System clinical trials who were implanted with an intracranial brain stimulator for detecting and treating seizures. Participants kept a seizure diary, and changes in medications were logged. Using a wavelet transform, we extracted underlying multidien cycles from recordings of IEA. We identified timepoints where a new anti-seizure medication (ASM) was started and compared seizure rates among epochs with >50% amplitude reduction or steady multidien IEA cycles after beginning ASM. This measure was evaluated for predictive power by the area under the curve (AUC) of the receiver operating characteristic.

Results: We identified 168 new ASM trials, of which 63 (37.5%) led to a ≥50% decrease in seizure rate (responders). Relative seizure rate was significantly lower ($p<0.05$ Wilcoxon test) when the amplitude of multidien rhythms of IEA was reduced by >50% after introduction of a new ASM. When measuring the sensitivity-specificity trade-off of using decreases in multidien rhythms of IEA as predictor for reduction in seizures at a 3-month horizon, we found an AUC of 0.70-0.83 when predicting 50-90% reduction of seizure rate, respectively. The same method yielded an AUC 0.60-0.79 when predicting 50-90% seizure reduction at 6 months.
Conclusion: In this cohort, a >50% reduction of multidien cycles of IEA following the beginning of new ASM was consistently associated with reduced reported seizure rates for up to 12 months. Although causality cannot be established, this suggests that multidien IEA cycles may play an important role in seizure recurrence over long periods (months to years).

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Seizures as initial and predominant clinical concern in adult patients with STEC HUS

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Purpose: Hemolytic uremic syndrome belongs to thrombotic microangiopathies. The mentioned syndrome is mainly found in children, where neurological manifestations, especially seizures, often predominate. However, it is relatively rare in the adult population. The purpose of this study is to present and characterize cases where seizures are one of the initial and predominant clinical symptoms.
Method: The clinical information was collected from Central University Clinic and was evaluated retrospectively. Informed consent was taken from each of the patients.
Results: In total, 15 patients were selected. 10 patients were women and 5 were men. Age - 37 (SD - 10.33), hemoglobin - 8.4 g/dL (SD - 3.065), platelet count - 95.6 x 109 /L (SD - 30.26), creatinine level - 594 µmol/L (SD - 261.1), blood urea nitrogen (BUN)- 75.26 mg/dL (SD - 17.8), lactate dehydrogenase (LDH) - 172.8 U/L (SD - 56.62) In 90% of patients, vomiting and diarrhea were presenting symptoms, and soon after their onset (2-5 days) seizures occurred. The latter was the main clinical concern for the rest of the course, due to its severity and frequency. The EEGs of 8 patients with generalized tonic-clonic seizures showed diffuse delta slowing but no focal changes. None of them suffered a long-term neurological deficit or seizure disorder after their recovery. One of the four patients who had partial seizures had structural lesions on MRI. In three patients, the EEG showed focal spikes and slowing consistent with lateralization. It is important to note that seizures were well managed with benzodiazepines and the therapeutic response was satisfactory in virtually all cases.
Conclusion: It is important to note that although involvement of the nervous system in STEC-HUS is relatively rare in the adult population, these cases do occur and are often associated with severe seizures.

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Clinical phenotype similarities and differences with déjà vu and jamais vu focal aware seizures

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Purpose: Déjà vu (translated 'already seen') is a common epileptic aura associated with temporal lobe epilepsy (TLE). Jamais vu (translated 'never seen'), a feeling of unfamiliarity in a familiar situation, is a less common aura thought to have similar implications to déjà vu. As these phenomena are actually the opposite of one another, this raises the question of whether the clinical phenotypes and electrophysiological correlates also differ.
Method: Details of patients with déjà vu or jamais vu and video-EEG monitoring were obtained from the epilepsy electronic patient record at the national epilepsy monitoring centre at Beaumont Hospital, Ireland. Details of demographics, seizure semiology, EEG monitoring and imaging findings, and outcomes were examined. Results were compared using independent t-test and chi-squared tests.
Results: Thirty-three patients with déjà vu and 5 with jamais vu were identified (4 with video EEG). Patients with déjà vu had a higher rate of interictal slowing than those with jamais vu (73% vs 20%, p=0.021). There was no difference in age, sex, handedness, history of epilepsy surgery, response to medications, or psychiatric history.
Where ictal activity was localised, 37% of the déjà vu and 50% in the jamais vu group were to the left temporal lobe, while 43% and 50% respectively were to the right temporal lobe.
A similar proportion were seizure free (21% vs 20%) after standard temporal lobectomy.
Conclusion: Patients with jamais vu have a similar clinical phenotype and surgical outcomes to patients with déjà vu, despite these phenomena being linguistic opposites. Those with jamais vu were less likely to have focal slowing or sharp waves, or have extra-temporal involvement on ictal recordings, suggesting a deep origin. Some patients with déjà vu had alternative diagnoses such as frontal lobe epilepsy, generalized epilepsy, or NEAD, so it may be a less-specific seizure type than jamais vu for TLE.

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Using seizure cycle forecasts to identify optimal monitoring timeframes and improve the diagnostic yield of vEEG

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Purpose: A difficulty of video-electroencephalography (vEEG) is scheduling monitoring sessions to adequately capture epileptic activity (interictal discharges and/or seizures). This study examined whether personalized forecasts of seizure risk can improve the diagnostic yield of vEEG. Seizure risk forecasts were validated across a large database of ambulatory vEEG studies, followed by a prospective cohort study to schedule vEEG based on personalized forecasts.
Method: The validation study included adults diagnosed with epilepsy who underwent ambulatory vEEG monitoring (Seer Medical). Studies with no forecast ('baseline group', n = 3587) were compared to studies where vEEG occurred during a timeframe deemed high-risk ('high-risk group', n = 305). High-risk periods were determined using seizure cycles estimated from an individual's self-reported event times. The proportion of cases where a high-risk forecast corresponded with epileptic activity relative to the baseline group was examined (using Risk-Ratios (RR) and Test of Proportions). For the prospective study, thirty-five adults diagnosed with epilepsy (>1 seizure/month) referred for vEEG were recruited. After ~6 months (or 10 seizures), follow-up vEEG was scheduled during high-risk. Outcome measures: EEG report (abnormal/normal) and clinical seizures during monitoring.
Results: In the validation study, the high-risk group was 25% more likely to have an abnormal report relative to baseline (190/305: 62.3% vs 1790/3587: 49.9%, RR = 1.25, 95% CI, 1.137 to 1.370, $p < 0.001$) and 63% more likely to present with clinical seizures during vEEG monitoring (56/305: 18.4% vs 424/3587: 11.3%, RR = 1.63, 95% CI, 1.265 to 2.101, $p < 0.001$). In the prospective study to-date, 11/35 participants completed their scheduled vEEG, with 75% of those in forecast high-risk presenting an abnormal report.
Conclusion: Forecast high-risk periods correspond with increased likelihood of capturing epileptic activity during monitoring. Prospective findings provide preliminary support for applying seizure cycle forecasting to schedule and optimize diagnostic yield of vEEG.

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Two cases of extremely delayed Lennox-Gastaut syndrome diagnosis

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Purpose: Lennox-Gastaut syndrome (LGS) is a developmental and epileptic encephalopathy, characterized by multiple types of drug-resistant seizures, cognitive impairment, generalized slow spike-wave (SSW) discharges, and generalized paroxysmal fast activity (GPFA).
Method: Patient 1. A 35-year-old male started to have atonic seizures and cognitive delay at the age of 8. The diagnosis of "Generalized absence epilepsy" was made. At the age of 10, tonic seizures began. Frequency of all types of seizures increased with age. Seizure freedom

wasn't achieved on FT, VPA, LTG, and LCM.
Patient 2. A 44-year-old male with the disease onset at 3 years of age had atonic seizures up to 30 times a day. Later, bilateral tonic-clonic seizures and myoclonia appeared. There was a marked cognitive impairment. Throughout his life he was diagnosed with: "Idiopathic generalized epilepsy", "Myoclonus epilepsy", and "Cryptogenic epilepsy with atonic seizures". CBS, ETS, PB, and VMA didn't have any effect on seizures.
Patients underwent long-term video-EEG recording (LTM).
Results: On LTM, patterns of GPFA and generalized SSW were seen. Atypical absences were captured in patient 1. He also had generalized tonic seizures, sometimes very subtle. Patient 2 had various types of epileptic seizures on LTM including atypical absences, myoclonic seizures, and generalized tonic seizures.
In patient 1 with a shorter duration of the disease, LGS EEG patterns were evident. In patient 2 these patterns had altered morphology.
The diagnosis of LGS was then first made. Therapy was adjusted accordingly with ketogenic diet and Rufinamide. VNS implantation was also considered.
Conclusion: If LGS for some reason wasn't diagnosed in childhood, it can be difficult to diagnose later. In our cases, disease duration at the moment of diagnosis was 27 and 43 years. Adult neurologists are often not sufficiently informed about pediatric epileptic syndromes which can lead to inadequate treatment.

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Increased serum Calponin-3 is a potential biomarker in patients with epilepsy

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Purpose: To assess whether serum calponin-3 could serve as a biomarker for epilepsy.
Method: We collected serum samples from 242 subjects, including 157 patients with epilepsy and 85 healthy control subjects. The levels of serum calponin-3 were determined using enzyme-linked immunosorbent assay kits (ELISA), and their correlation with epilepsy clinical characteristics was analysed statistically. We used the upper limit of the 95% confidence interval (CI) when dividing epilepsy patients into normal and elevated groups based on serum calponin 3 levels in controls. The receiver operating characteristic (ROC) curve was used to determine the diagnostic efficiency.
Results: There was a significant increase in serum calponin-3 levels in patients with epilepsy (14.76 ng/ml; 95% CI, 14.41 to 15.12) compared with healthy controls (12.72 ng/ml; 95% CI, 12.16 to 13.29, $p < 0.001$). Serum calponin-3 levels had a significantly positive correlation with disease duration ($r = 0.342$, $p < 0.001$) and number of seizures ($r = 0.576$, $p < 0.001$) in epileptic patients. Moreover, compared with patients with normal serum calponin-3 levels, those with elevated calponin-3 had a younger onset age (median (25–75th percentiles), 24 (15–43.5) *vs*. 18 (13–28.5)), a longer disease duration (0.42 (0.17–4.54) *vs*. 3.13 (1.25–7.79)) and more seizures (4 (3–5.5) *vs*. 8.5 (5–12)). According to the ROC curve, the sensitivity and specificity of serum calponin-3 in the diagnosis of epilepsy were 76.43% and 63.53% (area

under the ROC curve (AUC) = 0.727; 95% CI, 0.689 to 0.796, $p < 0.001$), respectively, when the cut-off value was 13.56 ng/ml, and in the diagnosis of generalized seizures were 85.71% and 63.53% (AUC=0.802; 95% CI, 0.730 ~ 0.874, $p < 0.001$), respectively, when the cut-off value was 13.57 ng/ml.
Conclusion: Increased serum calponin-3 might be a candidate biological marker of epilepsy in clinical assessment.

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Mosaic recurrent *MTOR* pathogenic variant in a patient with stable sleep related frontal lobe epilepsy despite striking progression of diffuse cortical and subcortical T2 hyper-intensity MRI

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Purpose: We present a 32 year old patient with sleep-related focal to bilateral tonic-clonic seizures arising from the left frontal lobe commencing at 18 years of age. Initial MRI was considered normal. Despite a stable clinical course and examination, progressive MRI changes were observed over 14 years, involving extensive ill-defined cortical and subcortical T2 hyper-intensity of the entire left cerebral hemisphere with gyral expansion.
Method: High resolution MRI, histopathological analysis, deep gene panel and exome sequencing, and droplet digital PCR were employed to characterise the clinical progression and molecular architecture.
Results: Serial MRI imaging confirmed enlargement of the lesion over a 12-year period during early adulthood. Histopathological analysis of a left frontal lobe biopsy involving cortex and white matter showed features (e.g., dysmorphic neurons, balloon cells) in white matter most suggestive of focal cortical dysplasia (FCD) type IIb. Genetic analysis of formalin-fixed paraffin-embedded brain tissue revealed a recurrent mosaic pathogenic MTOR missense c.4448G>A (p.Cys1483Tyr) gain-of-function variant at 8.5% variant allele fraction. The variant was not detected in peripheral tissue. This variant has been previously reported in patients with hemimegalencephaly (HME).
Conclusion: Our findings extend the spectrum of brain lesions associated with *MTOR* variants beyond stable FCDs and HMEs. Gain-of-function variants in mTOR pathway genes are the most frequently identified genetic cause of FCDs and HME, and are often mosaic in sporadic cases. mTOR hyperactivation leads to neuronal migration defects and development of focal

dysplasias which are typically static lesions. In our patient there is evidence of a progressive lesion on imaging, despite a stable clinical picture more consistent with a long term epilepsy associated tumour (LEAT). These findings may have significant clinical implications for this patient as LEAT may become malignant. The patient therefore requires monitoring with regular imaging long term.

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Late-onset rasmussen's encephalitis (LORE): three illustrative cases and literature review

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Purpose: Late-onset Rasmussen's Encephalitis (LORE) is as a rare uni-hemispheric progressive inflammatory disorder causing severe neurological dysfunction and drug-resistant epilepsy with onset during late adolescence or adulthood. Due to the scarce available evidence, we aim to improve its clinical characterization and summarize their distinctive features
Method: Three illustrative cases are presented including clinical, neurophysiological and neuroimaging work-up. Our findings are discussed with the previous evidence obtained through a comprehensive search.
Results: The patients reported had an adult-onset within a wide range of age. The first clinical manifestation was variable, including refractory focal epilepsy, progressive hemiparesis or *epilepsia partialis continua,* in line with previous findings. A progressive hemiatrophy with frontal or posterior predominance in MRI and an extensive hypometabolism in functional neuroimage were documented. A uni-hemispheric slow background activity and epileptiform discharges progressively developed during the long-term follow-up, as described in literature. According to European Consensus Diagnosis Criteria two of our patients met Part-A and one Part-B criteria. In consonance with previous publications, a slower neurological decline was observed with immunotherapy.
Conclusion: Despite the wide range of clinical manifestations at onset, overall, LORE has a milder neurological deterioration and favorable response to immunotherapy, which implies a better prognosis. Further studies are needed to clarify the best strategy.

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Different clinical manifestations of tuberous sclerosis complex in adults

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Purpose: Tuberous sclerosis complex (TSC) is a genetic disorder affecting mTOR pathway associated with formation of benign embryonic tumors in different systems and organs as brain, skin, lungs, heart, kidneys, eyes affecting their structure and function differently, at any age, usually starting from early childhood. The aim is to evaluate different clinical manifestation of TSC in adults. Timely start of precision medicine for TSC treatment may prevent some of the clinical manifestation seen in untreated adults.
Method: Seven adults with genetically verified TSC are evaluated clinically: their somatic, neurologic and psychologic functioning, and with electrophysiological and imaging methods.
Results: Six of seven patients with genetically verified TSC are classified as developmental epileptic encephalopathies, presenting with pharmaco-resistant epilepsy, four with severe intellectual disability and behavior problems of attention deficit and hyperactivity disorder (ADHD) and autistic spectrum disorder (ASD), two with mild intellectual disability. Only one male patient with a pathogenic mutation of the TSC2 gene and multiple brain tubers reports no seizures. Psychiatric symptoms of schizoaffective psychosis are the only clinical manifestations in this patient. Skin *angiofibroma* is present in six of seven patients, and lung lymphangioleiomyomatosis *(LAM) and* kidney *angiomyolipoma are* seen in one patient, resulting in kidney capsule rupture and the need for surgical treatment with nephrectomy. Despite the recommendation for precision medicine treatment that the commission should approve for rare diseases in the state health care system, most adult patients with TSC are treated with symptomatic pharmacological and surgical treatment.
Conclusion: TSC is a rare genetic disorder causing developmental epileptic encephalopathy, pharmaco-resistant epilepsy, intellectual disability, behavioral problems, psychiatric disorders and different somatic lung, hearth, kidney, skin disorders if untreated. Early screening for TSC and precision medicine treatment with everolimus, may prevent the progression of the clinical picture from childhood to adulthood.

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Levetiracetam-induced psychosis in a patient with history of non-epileptic seizures

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Purpose: To highlight the possible association between Levetiracetam-induced psychosis and a history of psychogenic non-epileptic seizures.
Method: Case report of a young female patient who developed acute, reversible psychosis, three days after initiation of treatment with Levetiracetam.

Results: A 25-year-old female, with a history of non-epileptic events since early childhood (that had been inconsistently interpreted as either psychogenic non-epileptic seizures, parasomnia or frank epilepsy for which she received a whole array of AEDs), was admitted to our clinic for evaluation of a new type of paroxysmal episodes over the past year, at a frequency of up to 10 episodes/day. Video EEG recording confirmed those episodes to be of epileptic origin, prompting initiation of Levetiracetam 250 mg qd, with dramatic improvement in seizure frequency from the second day of treatment. On day four, however, the patient started having hallucinations and delusions and became extremely agitated and aggressive. Levetiracetam was stopped and the patient responded to low doses of Risperidone, with full return to baseline behavior after 48 hours. In the long run, the patient remained psychosis-free and was put on Carbamazepine for control of her seizures.
Conclusion: While forced normalization following seizure control may underlie interictal psychosis, such events are characteristic of long-standing epilepsy, which was not the case of our patient. Rather, a prior history of psychogenic non-epileptic seizures, even in the absence of current psychiatric disturbances, could be a risk factor for Levetiracetam-induced psychosis and this antiepileptic drug should be used with caution in such patients.

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Value-based care delivery to patients with epilepsy and intellectual disability, before and after the initiation of an epilepsy outreach service: a six year review

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Purpose: In 2017, the epilepsy service from St James's Hospital Dublin, developed an outreach service for patients with intellectual disability and epilepsy living in a residential care facility. The goal of this outreach service is to provide value-based patient-centred care by improving patients' experience while reducing costs and providing remote follow up. The aim of this review was to evaluate outcomes of the implementation of this model of care.
Method: The number and type of clinical interactions before and after the 2017 outreach clinic establishment and cost savings associated with these were reviewed. We compared this model of care to the traditional hospital outpatient service. We assessed the number of clinical interactions - outpatient department visits, telephone encounters and Emergency Department attendances to St James's Hospital- in the three years before the 2017 outreach clinic with those in the following three years.
Results: The main findings of this review were that following the implementation of the outreach clinic, there was approximately a three-fold reduction in OPD visits and a similar increase in the number of telephone encounters with the epilepsy service. This suggests a partial transition to virtual care, which translates into an improvement in quality of care,

considering that a telephone encounter provides a less distressing patient experience than a hospital attendance, and significant cost savings.
Conclusion: Our findings suggest that a model of care that consists of outreach visits and telehealth pathways will reduce unnecessary hospital visits and possibly decrease costs. The benefits of this model of care were further highlighted in the context of the recent COVID 19 pandemic and the related healthcare restrictions. We hope this model of care for patients with intellectual disability in residential care settings will be replicated to other neurological or medical conditions.

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A prospective observational study on understanding of idiopathic generalized epilepsies namely juvenile myoclonic epilepsy and epilepsy with generalized tonic-clonic seizure alone by electroencephalogram with updated terminology in a tertiary care hospital

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Purpose: Aim of the study was to identify the differences between juvenile myoclonic epilepsy and epilepsy with generalized tonic-clonic seizures alone by semiology and EEG with updated terminology under the observation of the clinicians.
Method: This was a prospective observational study and was conducted in the epilepsy clinic, department of neurology, Bangabandhu Sheikh Mujib medical university, from February 2021 to July 2022. The sample size was 60
Results: Among 60 patients, family history was present in 12 (20%) and 6 (10%) JME and GTCA patients, respectively. In this study, the EEG finding of generalized spike-wave (2.5-5.5 Hz) was seen in 26 (43%) and 19 (32%) among JME and GTCA patients, respectively. Generalized Polyspike wave (2.5-5.5 Hz) was seen in 26 (43%) JME patients, and EEG was normal in 15 out of 60 patients of epilepsy. In EEG findings, 2.5-5.5 Hz generalized spike-wave should be diagnosed in JME and GTCA patients as a special group of IGEs.
Conclusion: In this study, we have recognized and differentiated between juvenile myoclonic epilepsy and generalized tonic-clonic seizures alone by semiology and EEG in IGE syndromes as a special grouping among the IGEs is helpful as they carry prognostic and therapeutic implications.

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A prospective study on stress biomarkers in adult patients with drug resistant epilepsy on a modified Atkins diet

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Purpose: Ketogenic diets like the modified Atkins diet (MAD) are increasingly used in patients with drug resistant epilepsy. For epilepsy patients, stress is a well-known seizure-precipitating factor. New possibilities in measuring biomarkers of stress are now available. The purpose of this study was to investigate the impact of MAD on selected endocrine stress biomarkers.
Method: Forty-nine patients with drug resistant epilepsy were investigated at baseline and after 12 weeks on MAD. Cortisol and cortisol binding globulin (CBG) were measured and free cortisol index (FCI) calculated. We also measured metanephrine, normetanephrine and methoxytyramine, all markers of epinephrine, norepinephrine and dopamine, respectively. Changes were analyzed according to sex and category of anti-seizure medications (ASMs). The different markers at baseline and after 12 weeks of MAD treatment were correlated with seizure frequency.
Results: The change in total cortisol was modest after 12 weeks on the diet (from 432.9 nmol/l (403.1 – 462.7, 95%CI) to 422.6 nmol/l (384.6 – 461.0), p=0.6). FCI was reduced (from 0.39 (0.36 – 0.42) to 0.34 (0.31 – 0.36), p=0.001). CBG increased during the study period (from 1126.4 nmol/l (1074.5 – 1178.3) to 1272.5 nmol/l (1206.3 – 1338.7), p<0.001). There were no changes in the metanephrines after 12 weeks on the diet. The decrease in FCI was significant only in women, and only observed in patients using non-enzyme inducing ASMs. We did not find any correlation between cortisol, CBG or FCI levels and seizure frequency.
Conclusion: After being on MAD for 12 weeks, FCI decreased significantly. The reduction in FCI may reflect reduced stress, but it may also be an effect of increased CBG. The reasons behind these alterations are unknown but may possibly be a result of a reduction in insulin resistance and thyroid hormone levels. Treatment with MAD does not seem to influence "fight and flight" hormones.

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Tuberous sclerosis in adulthood: focus on transition and epilepsy prognosis

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Purpose: To describe the prognostic predictors in a cohort of adult patients with tuberous sclerosis complex (TSC).
Method: Retrospective analysis of patients diagnosed with TSC according to the updated international diagnostic criteria[1]. All underwent a comprehensive electro-clinical work-up. Student's t-test and Fisher's exact test were used to compare variables among the Remission and Non-Remission group.
Results: We selected 41 patients with TSC and CNS involvement in terms of epilepsy and/or brain lesions, attending the Epilepsy Center of our Institute: of them, 16 (39%) were in transition from the pediatric care and 5 (12.2%) were referred by other specialists. Multiorgan involvement includes cutaneous (85.4%), nephrological (69.2%), hepatic (38.5%), cardiac (25.7%) and pneumological (25%) manifestations.

Thirty-seven patients (90.2%) had epilepsy (M/F:18/19, mean age 34.5±12.2 years). Among them, 22 (59.5%) had intellectual disability/borderline IQ, 21 (56.8%) psychiatric/behavioral disorders. The mean age at seizure onset was 3.7±7.5 years: most (29, 80.5%) presented with spasms/focal seizures by age 3 years, only 2 (5.4%) had seizure onset in adulthood. Most cases (25, 67.6%) experienced multiple seizure types during their disease history. Thirty-one (83.8%) had multiple disease-related findings at brain MRI, besides cortical tubers. Of the 30 patients tested, 9 (30%) disclosed pathogenic variants in *TSC1*, 16 (53.3%) in *TSC2*, 5 (16.7%) were negative. At last assessment, 12 (32.4%) were seizure free (remission group) and 25 (67.6%) had drug-resistant seizures (non-remission group). The non-remission group showed significant higher frequency of ID ($p=0.036$) and multiple seizure types ($p<0.001$) compared to the remission one.
Conclusion: Epilepsy is one of the most frequent neurological manifestations in TSC, with drug-resistant seizures in 67.6% of cases. ID and multiple seizure types are predictors of poor prognosis. In few paucisymptomatic cases, the diagnosis of TSC can also be made in adulthood. Cutaneous and nephrological manifestations require continuous specific follow-up in adults.

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EMU findings in presumed lesional focal epilepsy

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Purpose: The success of epilepsy surgery is dependent on the ability to remove the epileptogenic zone. When brain imaging reveals an epileptogenic lesion - such as a cavernoma - it is usually presumed that the lesion is the cause of the epilepsy. However, it is imperative the video-EEG findings are concordant with the location of the focal presumed epileptogenic lesion. There are few published articles studying the prevalence of discordant EEG findings[1].
Method: All epilepsy monitoring unit (EMU) data from 2015-2022 were retrospectively analysed. Electrographic data were correlated with brain imaging (MRI and/or PET/CT).
Results: Through our EMU we identified many cases of focal lesions where EEG data were discordant from imaging. Further results will be discussed at the conference.
Conclusion: In a significant fraction of patients with epileptogenic lesions evident on brain imaging before EMU admission, subsequent video-EEG monitoring confirmed that the lesion was not the cause of the patient's active epilepsy.

[1] Nagarajan L, et al. Discordant electroencephalogram epileptiform activity and hemispherectomy in children with refractory epilepsy and encephaloclastic lesions: a case series. *Dev Med Child Neurol*. 2022;64(3):387-394. doi:10.1111/dmcn.15047

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Autonomic features of temporal lobe seizures in patients with successful epilepsy

surgery

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Purpose: Autonomic signs and symptoms (ASS) are frequent, although difficult to identify, clinical manifestations during temporal lobe seizures. The purpose of this investigation was to describe the frequency of ASS in patients with temporal lobe epilepsy (TLE) and their lateralizing value.
Method: We analyzed the frequency and predictive lateralizing value of ASS in 55 patients with TLE (34 left) who underwent successful epilepsy surgery (Class I, ILAE). ASS were defined according to the ILAE Glossary on seizure semiology and obtained from patient´s interrogation and videoEEG analysis. Fisher's test was used for statistical significance.
Results: We identified 13 ASS: sweating, paleness, hypersalivation, flushing, belching, spitting, tearing, nausea, ascending epigastric sensation, piloerection, thirst, urge to defecate, and flatulence. We found at least one AAS in 25 patients (45%), 2 ASS in 8 patients (14%), 3 and 4 ASS in 1 patient each. Ascending epigastric sensation (31%), nausea and hypersalivation (5%) and paleness (4%) were the most frequent ASS. Nausea occurred significantly more frequently on right TLE (p=0.02). We did not find lateralizing value in the rest of the ASS.
Conclusion: Although ASS are common in TLE, their detection should be based on careful interrogation and videoEEG analysis as they may go unnoticed. The identification of clinical manifestations continues to be a good non-invasive tool of great value in the definition of the epileptogenic zone in patients candidates for epilepsy surgery.

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Highly purified cannabidiol improves stability and postural tone in adult patients with Lennox-Gastaut syndrome: a case series

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Purpose: Lennox-Gastaut Syndrome (LGS) is a severe developmental epileptic encephalopathy associated with several neurological signs and symptoms. Impairment in postural tone and need of caregiver-assisted wheelchair is one of the main features of LGS patients, frequently attributed to recurrent seizures. Highly Purified Cannabidiol (CBD) is a novel antiseizure medication that received the recommendation for treating seizures, in combination with clobazam, in patients diagnosed with LGS. CBD can reduce the frequency of seizures, in particular drop seizures, in patients with LGS in both clinical trails and real-world studies. No data are available about drug effects on postural tone, locomotory activity, gait and stability in LGS.

Method: In this case series, three adult patients with a diagnosis of LGS and uncontrolled seizures were treated by CBD.
Results: After beginning the treatment, it has been noted small improvement in seizures frequency and, unexpectedly, an amelioration of postural tone and stability, which were measured using the validated Gross Motor Function Classification System.
Conclusion: Our case series suggest that CBD may help the management of patients with LGS not just in term of seizure control, but also considering other comorbidities, such as mobility problems (postural tone and stability). The mechanisms at the basis of this improvement may be related, other than seizure reduction, to the drug effect on the brain locomotor centres, as demonstrated in animal model studies.

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Examining the evolution of virtual epilepsy care in a post-pandemic clinical environment

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Purpose: Covid-19 presented unique challenges and opportunities in the delivery of efficient and patient-centred epilepsy management. Our institution (St. James's Hospital in Dublin) was transformed into a fully virtual (telephone, without video) service overnight. Pre-2020, 18% of patients' clinical encounters were virtual. Having entered the post-pandemic era, we want to examine how to deliver the most effective hybrid service.
Method: Our framework for effective virtual outpatient services was implemented in 2018 through a quality improvement project (QIP). An established virtual service aided a safe transformation to complete virtual care at the onset of the pandemic. Having transitioned back to a hybrid model (currently 50% virtual), we want to share our experience of optimising virtual care delivery.
Results: 3000 adult epilepsy patients actively attend our service. During the original virtual care implementation, patient feedback was mostly positive (91% patient satisfaction rate). Our current cohort of patients who receive virtual care is poorly selected and feedback from patients more mixed. Limitations appreciated intuitively, as well as identified by patients and clinicians, are being confirmed with early data. Informed by our experience of virtual care delivery during the pandemic, we are developing a hybrid model of integrated virtual and in-person care.
Conclusion: Although our pre-pandemic QIP provided an advantage to the delivery of virtual care during the pandemic, further developing virtual care in the post-covid era is an ongoing process with the aim of delivering individualised patient centred care in a safe manner. Sharing this experience will help other services in the development of their virtual care delivery.

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High-precision individualized approach in drug-resistant epilepsy patients using Ultralong term EEG monitoring (UNEEG)

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Purpose: Accurate seizure detection is crucial for assessing risk and improving epilepsy management. Patient-reported dairy seizures are the primary method for monitoring epilepsy, but it is not always reliable. Patients describe seizures in diaries that may not be actual seizures, while others fail to report genuine seizures because they go unaware. Ultralong term EEG monitoring (UNEEG) enables continuous remote EEG recording and provides an accurate assessment of seizures in real-life 24/7/365. This work aimed to use UNEEG devices in a group of patients in whom it was impossible to know the real burden of seizures to make appropriate therapeutic decisions.
Method: We implanted UNEEG in 3 patients with refractory epilepsy in whom the actual number of seizures could not be determined. Case 1 is a 38 y.-o. patient with right posterior quadrant epilepsy with the coexistence of psychogenic nonepileptic seizures (PNES) and subclinical epileptic seizures after undergoing epilepsy surgery. Case 2 is a 53 y.-o. female patient who lives alone with left posterior quadrant epilepsy (PQE), inoperable by location, and unaware of her seizures many of which are nocturnal. Case 3 is a 31 y.-o. male patient with a left PQE and coexistence of PNES and language barrier.
Results: The information provided by the UNEEG device proved decisive for the treatment. Considered as a whole, the UNEEG system made it possible for patients unaware of seizures to optimize treatment based on accurate information. In patients with the coexistence of epilepsy and PNES, it allowed an improvement for the patient for the differentiation and a pharmacologic focusing on epileptic events. It was also possible to determine the circadian rhythm of seizures.
Conclusion: In conclusion, UNEEG allows, in defined indications, to determine the epileptic burden, to optimize treatment based on accurate data to reduce seizures, improve QoL and, eventually, reduce morbidity and mortality in refractory epilepsy.

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Retrospective analysis of treatment effectiveness newly diagnosed epilepsy with focal seizures in adults

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Purpose: The retrospective analysis focuses on therapeutic effects achieved in 862 adult patients aged 16-90 years of life with newly diagnosed epilepsy with partial seizures treated by the author in the years 1988 to 2018 and subjected to at least 2-year-long follow-up focusing on therapeutic effects.

Method: The analysis of therapeutic effectiveness was based on the etiology of epilepsy, the course of disease until the start of treatment and the type of antiseizure classic or new generation pharmaceuticals used in the treatment.
Results: The outcome of the first monotherapy of epilepsy in the group of patients with partial epilepsy depends on the: type of epilepsy and is the most effective in treatment of idiopathic epilepsy, age of the patient and is the most effective in the elderly subjects and patients up to 20 years of life, number of seizures since the introduction of antiseizure therapy and is the least effective in the group with more than 6 seizures. The outcome of the first monotherapy resulting in the percentage of remission equaling 52.2% does not depend on the type of the introduced antiseizure medication.The reason of failure due to ineffectiveness of an antiseizure agent depends on the type of the employed medication: in paired comparisons - VPA>PB and VPA>PHT, in concomitant comparisons – additionally VPA>CBZ, VPA>LTG and PHT<LEV. Early add-on therapy introduced after the first therapeutic failure is clearly significantly more efficient that medicine substitution. Of the nine investigated prognostic factors, the effectiveness of the first monotherapy depends solely on status epilepticus being the initial manifestation of the disease. Almost 19% of patients with refractory epilepsy achieve remissions when treated with two- or three-drug combinations.
Conclusion: The general prognosis of achieving remission of epilepsy after 2 years of treatment is good: 72.2% of patients are seizure-free.

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Looking beyond post-ictal generalised EEG suppression - the role of infra-slow shifts on the mechanisms of SUDEP

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Purpose: Patients with refractory epilepsy have a higher risk of sudden and unexpected death (SUDEP), particularly if they suffer frequent bilateral to tonic-clonic seizures (BTCS). The mechanisms of SUDEP remain unknown, the association between post-ictal generalised EEG suppression (PGES) following BTCS and SUDEP risk has been raised. In SUDEP animal models the presence of spreading depolarisation, a slowly propagating suppression of neural discharge was fatal when reaching the brainstem. Here, we explore the presence of infra-slow shifts (IS) in human intracranial EEG during post-ictal phase and the relation to PGES.
Method: We retrospectively analysed stereo-EEG studies performed at the National Hospital of Neurology and Neurosurgery between 2015-2020. PGES was defined by presence of post-ictal EEG with <10µV in all available contacts.
As SEEG was recorded with AC amplifiers (SD LTM 64 Express – Micromed®), post-processing

step using an equalizer was applied. Visual inspection of the post-ictal EEG was then performed (0.008-0.1Hz bandpass filters).
Results: BTCS were recorded in 13/90 studies (14%); mean patient age was 31 years (range 20-46; 6 male). 4 studies were excluded (grid implantation, artefactual EEG), and 9 BTCS in 9 patients were available.
PGES was present in 3/9 seizures, with a 35 second average duration (range 30-41). IS was observed in 5/9 seizures, with an average duration of 28 seconds (range 20-32) and was concomitant with PGES in 2/3.
IS was detected in the hippocampus (3/5) and amygdala (3/5). Analysis also included structures as orbitofrontal region (8/9 cases), cingulum (8/9 cases) and insula (7/9 cases). There was no relationship between seizure onset and the presence of IS.
Conclusion: This initial investigative work found IS exclusively in hippocampus and amygdala, highlighting that these may play a role in mediating suppression following seizures. Although, the same structures were investigated, PGES was not always associated with IS, which may indicate a distinct mechanism.

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Migrating postictal MRI changes masquerading as brain tumor in LGI1 encephalitis with status epilepticus

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Purpose: The objective of this study is to demonstrate the migrating Magnetic Resonance Imaging (MRI) lesions in a patient with Leucine-rich glioma-inactivated 1 (LGI1) antibody encephalitis masquerading as a brain tumor or focal dysplasia.
Method: The patient is 43 years old male with a history of recurrent episodes of speech blockage, left head deviation and pulling sensation to the left side, left upper extremity pilo-erection and confusion; The Interictal EEG was normal and MRI brain was normal. He was diagnosed as focal epilepsy and was started on Levetiracetam, then Oxcarbazepine was added due to the worsening of his symptoms; the patient presented to our hospital in Status Epilepticus with recurrent generalized tonic clonic seizures and no recovery to baseline. He was given Valproic acid, Levetiracetam, Lacosamide and Perampanel.
Results: The patient had a lumbar puncture; MRI brain showed left amygdala enlargement and right inferior parietal cortex thickening suspicious of low grade glioma or focal dysplasia, and left posterior cingulate T2 hyperintense lesion. High dose IV steroids was started. MRI brain repeated in one month then 6 months showed bilateral hippocampal atrophy consistent with Mesial temporal sclerosis. MR Spectroscopy and Full body CT scan were normal. The autoimmune panel was positive for LGI1 antibody encephalitis. He received another course of Steroids and Plasmapheresis and he recovered to baseline with occasional short term amnesia 6 months after seizures onset. ASM were gradually tapered and he is currently treated

with Perampanel.
Conclusion: This case illustrates changing MRI features in LGI1 encephalitis presenting with seizures and status epilepticus. These changes are due to transient brain MRI abnormalities following seizure activity and should not be mistaken for low grade glioma or focal dysplasia.

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Patterns of evolution in drug-resistant epilepsy (Preliminary study)

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Purpose: To determine the presence of variations in the response to drug treatment in patients with drug-resistant epilepsy (DRE) over time, and to evaluate clinical factors potentially associated with these changes.
Method: 20 patients (13F, 7M) who attended the epilepsy clinic for a period of at least 5 years, and who met the DRE criteria at least once during that period were included. Demographic and clinical variables associated with their epilepsy were obtained and entered into a database. The frequency of seizures associated with the treatments was also obtained for each consultation, which was then graphed to analyze their variability over time.
Results: The mean age was 41 years (between 21 and 73 years). The mean ages of onset and duration of their epilepsy were 10 and 31 years, respectively. The vast majority were focal epilepsies, of structural cause, with lesional MR in 73% of cases. Two of them received epilepsy surgery. Regarding the evolutionary patterns, 65% presented sustained refractoriness, 20% in relapses and remissions, and only 15% achieved crisis freedom in a sustained manner. There was a tendency that all generalized epilepsy patients presented with sustained refractoriness, and all that achieved prolonged remission presented a lesional MR, without statistical significance given the low number of patients because it was a preliminary study.
Conclusion: It was possible to identify the different patterns of evolution of DRE, predominating that of sustained refractoriness. It was possible to link, in a non-statistically significant way, clinical variables such as the type of epilepsy and its etiology with the type of evolutionary pattern.

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Seizure response to cenobamate therapy correlates with plasmatic concentration, not daily dosage

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Purpose: Cenobamate is a recently approved anti-seizure medication (ASM) indicated for people with epilepsy (PwE) who is not responsive to multiple ASM trials. Early experiences suggest to us that cenobamate may show clinical efficacy even below the minimum daily dosages established by data sheet, perhaps because of the complex pharmacokinetic interactions it is able to induce. The aim of the study is to test the hypothesis that cenobamate plasmatic concentration could be clinically more informative than daily dosage about its efficacy.
Method: We conducted a multicenter study at University Hospital Foundation Campus Bio-Medico of Rome and at University of Salerno. We enrolled 25 Pwe (9 females, median age 24, 16-58-years-old), median ASM 3 (2-4), 9 with VNS, median age at onset 7 (1-41), median epilepsy duration 30 (5-56yy), 11 with psychiatric comorbidity and 16 with cognitive disability. Clinic variables and blood samples were collected before and 3 months after cenobamate therapy.
Results: Median seizure frequency (N of seizure in 2 weeks) was 9 (4.5-55) before cenobamate. After 3 months, median Cenobamate daily dosage was 150 mg (150-250), cenobamate plasmatic concentration was 17.6 (6.9-29.6) mcg/ml. Median seizure frequency was reduced to a 4.5 (0-13.7). Sixteen out of 25 (64%) Pwe were seizure responders (>50% seizure reduction) and 5 (20%) were seizure free. Median seizure reduction was 57.5% (-48 to 100%). Seizure reduction was directly correlated with plasmatic level of cenobamate (Spearman's rho 0.571, p=0.003), while was not correlated with daily dosage of cenobamate.
Conclusion: In our cohort, plasmatic level of cenobamate revealed to be highly informative of seizure response to cenobamate therapy. Our findings strongly encourage further studies to clinically validate the correlation between cenobamate plasmatic level and clinical efficacy, which could be of outstanding relevance in assisting clinicians managing the complex pharmacokinetic of cenobamate.

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The association between febrile seizure and Mesial temporal sclerosis in case of temporal lobe epilepsy, prospective observational study

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Purpose: Several studies have shown a significant relationship between a history of prolonged febrile seizure in early childhood and mesial temporal sclerosis. The probable mechanism of histopathological change in Mesial temporal sclerosis (MTS) is quite controversial. The possibility of hippocampal damage in early febrile seizure leads to mesial temporal sclerosis in temporal lobe Epilepsy. So, aim of the study was to evaluate the clinical association between febrile seizure and Mesial temporal sclerosis in

case of temporal lobe Epilepsy by the observation of clinicians.
Method: Prospective-cross sectional observational study was done in epilepsy clinic, department of Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from February 2021 to May 2022. This study was done among 84 patients. MRI of the brain with epilepsy protocol were used to detect mesial temporal sclerosis from radiology department of BSMMU & also different radiological department outside of BSMMU.
Results: This study was done among 84 patients with TLE, Age range 18-60 years. Among 58 TLE (69%) patients were MTS by MRI of the brain. Among them 38 (45%) patients had positive history of febrile seizure. MRI of the brain with epilepsy protocol were used to detect mesial temporal sclerosis from radiology department of BSMMU & also different radiological department outside of BSMMU. MRI have shown that febrile seizure can produce hippocampal sclerosis and hippocampal atrophy. These changes happened both unilaterally and bilaterally.
Conclusion: There is a clinical association between febrile seizure and Mesial temporal sclerosis in case of temporal lobe Epilepsy.

1227

Science or fiction; living in extremes of the universe (space and under the sea) even with epilepsy: a systematic review

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Purpose: The current systematic review aimed to investigate whether living under the sea or in space is detrimental for patients with epilepsy (PWE). We hypothesized that living under such conditions may predispose PWE to experience seizure recurrence by altering their brain function in a way that predisposes them to seizures.
Method: This systematic review is reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. On October 26, 2022, we systematically searched PubMed, Scopus, and Embase for relevant articles.
Results: Our endeavor yielded six papers. One study provided level 2 of evidence, while the rest of the publications provided level 4 or 5 of evidence. Five publications were about the effects of space missions (or simulations), and one manuscript discussed the impacts of underwater experience.
Conclusion: Currently, there is no evidence to make any recommendations about living in extremes of the universe (space and under the sea) with epilepsy. The scientific community should invest more time and effort in comprehensively investigating the potential risks associ-

ated with missions and living in such conditions.

1255

Autonomic dysfunction is more prominent in people with epilepsy and comorbid psychogenic non-epileptic seizures

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Purpose: People with epilepsy as well as people with psychogenic non-epileptic seizures (PNES) are prone to have interictal autonomic dysfunction that might contribute to an unfavorable outcome and an increased risk of premature death. We aimed to evaluate autonomic cardiovascular regulation in patients with epilepsy and comorbid PNES (PNES+) compared to patients with epileptic seizures only (PNES-) and healthy controls.
Method: We conducted case-control study (1:2) with gender and age matched participants. All patients underwent neurological and psychiatric examinations, EEG/video-EEG-monitoring, and brain imaging. In 13 PNES+ patients (mean age 32.2 ± SD 11.5 years, 9 women, 4 men), 26 PNES- patients, and 26 healthy volunteers, we recorded RR-intervals (RRI), beat-to-beat systolic blood pressure (BPsys), and respiratory frequency during 5 minutes at supine rest, upon and 5 minutes after active standing. We calculated RRI-standard-deviation (RRI-SD), RRI-coefficient-of-variation (RRI-CV), total-RRI-powers (RRI-TP) reflecting total cardiac autonomic modulation, low-frequency-powers of RRI-modulation (RRI-LF) and of BPsys-modulation (BPsys-LF) reflecting sympathetic modulation, high-frequency-powers of RRI-modulation (RRI-HF) reflecting parasympathetic modulation, supine and standing baroreflex sensitivity (BRS), and RRI-30:15-ratio reflecting baroreflex response to active standing. We compared autonomic parameters between PNES+, PNES-, and control groups (Kruskal-Wallis test and post-hoc Mann-Whitney-U-tests for differed parameters; significance: $p<0.05$). Data are presented as median and interquartile ranges.
Results: We revealed significant differences in all calculated parameters except for orthostatic BPsys-LF between the three groups. Compared to controls, PNES- patients had supine RRI-SD, RRI-CV, RRI-TP, RRI-LF, RRI-HF, BPsys-LF, BRS, and RRI-30:15-ratio decreased, while PNES+ patients had all the parameters decreased expect BPsys-LF. PNES+ patients, compared to PNES-, had all the orthostatic parameters decreased, the most significantly BRS (4.5[3.8; 5.8] vs 7.8[5.3; 9.9], $p<0.001$), with comparable BPsys.
Conclusion: Patients with epilepsy had impaired interictal autonomic cardiovascular regulation. Autonomic dysfunction was more severe in patients with than without PNES.

“Moscow Center for Innovative Technologies in Healthcare” supported the study (grant 2412-

45/22).

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Antihypertensive drugs in stroke patients: a new approach for treating post-stroke epilepsy

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Purpose: Stroke is the most common cause of seizures in patients >60 years. About 50% of new epilepsy diagnosis in elderly patients is associated with a brain ischemic event. Among the risk factors for epilepsy and stroke, hypertension is a prominent one. About 2% of patients with epilepsy have hypertension. In addition, hypertension seems to promote the development of seizures in the general population and increases the incidence of epilepsy in post-stroke patients. According to the European Society of Cardiology guideline, Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blocker (ARBs) drugs should be considered as first-line treatment of hypertension. ACEi and ARB seem to promote a protective effect in the development of seizures in the general population. However, no data are available about their possible preventive role in post-stroke epilepsy (PSE). In this pilot study, we evaluate the effectiveness of anti-hypertensive treatment in preventing PSE.
Method: In this pilot retrospective, observational study, patients with hypertension and diagnosis of ischemic stroke confirmed by clinical and neuroimaging evaluation were retrospectively selected between January 2016 and December 2022. Diagnosis of PSE was made according to ILAE criteria. The details of the anti-hypertensive treatment as well as demographics, and clinical and neuroradiological data were reviewed.
Results: 361 patients (mean age 70.2 ± 13.5 , 200 men, 58%) were enrolled. Twenty-seven (7.5%) patients developed PSE. Large vessel occlusion (p=0.031), atrial fibrillation (p=0.033), and cortico-sottocortical lesions (p=0.003) were related to a higher risk of PSE development. A lower risk of PSE was observed in patients treated with ARBs (p=0.027). No differences were observed according to ACEi, Calcium Channel Blocker, and Beta-blockers.
Conclusion: ARBs show a potential protective role in epilepsy development in patients with hypertension and stroke. If confirmed by larger studies, these findings suggest ARBs could be used as a novel approach for preventing epilepsy in patients with stroke.

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Assessment of electroencephalograpic response in different types of physical activ-

ity and relaxation techniques in patients with epilepsy

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Purpose: Patients with epilepsy present changes in their physical activity and relaxation techniques. The impact of the frequency of seizures and increased epileptiform discharges (ED) remain controversial, demonstrating a reduction in most studies.
Method: Quasi-experimental study, in adults with active epilepsy (patients undergoing pre-surgical evaluation and outpatients the epilepsy clinic). A standardized protocol under EEG monitoring was applied, including 5 periods of 15 minutes: rest with eyes open (baseline); aerobic exercise: modified Ruffier-Dickson (AE); post-exercise (PE); active relaxation technique (AR): Jacobson and Biofeedback; post AR. IEDs were counted in 3-minutes time windows exploring significant differences between periods through ANOVA, and between rest and each period through 95% CI of the difference, for each patient. Thvariation of the heart rate of the operationally predefined aerobic exercise was analyzed as adequate or insufficient, using the Chi-square test (a=0.05).
Results: We included 20 patients (M11/F9), age 30+ 7 years old (17-45), 18 with focal epilepsy,1 generalized and 1 undetermined; 11 (55%) with drug-resistant epilepsy at the time of the study. Monthly seizure frequency: median 20 (1-120). Usual physical activity (IPAQ): 6 sedentary, 6 light, 8 moderate.
Among 13 patients with IEDs, 8 showed modulation. Compared to rest. Significant inhibition was seen in 3 during AE and in 1 post-AR; activation occurred during AR (1) and post-AR (1). In the interindividual comparison, 5 activated post-EA), 2 inhibited Post-AR vs AR. Another patient under medication reduction presented a seizure during post-AR. In relaxation techniques, 3 patients with insufficient cardiac coherence presented low variability of less than 25% (p: 0.013).
Conclusion: Different types of activity in patients with epilepsy can cause IED modulation. there was inhibition in IED´s with rapid return to baseline in 20% of cases in this non-strenuous physical exercise protocol. Rarely did active relaxation techniques associate significant changes.

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Relative ictal immobility in focal seizures: a reliable sign of lateralisation?

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Purpose: Relative Ictal Immobility (RII) is an uncommon sign in focal epilepsy. It is defined as a

paucity of movement of one limb with purposeful or semi-purposeful movements in the contralateral limb. It has appeared in the medical literature since 1988 and has also been termed 'ictal contralateral paresis' or 'lateralised ictal paresis' by various authors. Despite this, there are few large cohort studies investigating its value as a clinical sign. In this study we aim to assess its utility in lateralising seizure foci, calculate its incidence in an Epilepsy Monitoring Unit (EMU) setting, and investigate any factors which may make RII more likely.
Method: A complete review of all recorded seizures in Cork University Hospital EMU 2014-2022 was carried out. We included all patients with proven epileptic seizures who were candidates for surgical intervention.
Results: Our data showed RII to occur in approximately 5% of our cohort, much lower than reported previously[1]. We found the sign to have high concordance with localising the seizure focus to the contralateral lobe, in keeping with the literature.
Conclusion: RII is a useful clinical sign in lateralising seizure focus, although large cohort data are lacking in the literature.

[1]Agarwal P, Kaul B, Shukla G, et al. Lateralizing value of unilateral relative ictal immobility in patients with refractory focal seizures--Looking beyond unilateral automatisms. *Seizure*. 2015;33:66-71. doi:10.1016/j.seizure.2015.08.009

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Epilepsy and employment: classification of workplaces and optimized legislation in Austria – a qualitative study

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Purpose: People with epilepsy face difficulties in obtaining or keeping employment. The question whether epilepsy must be disclosed during the application process is of central importance. We wished to determine personnel officers` and occupational physicians` view on this topic and to develop strategies for an optimized legislation regulating the management of medical details in the application process.
Method: Twelve personnel-managers and five occupational health-practitioners underwent a telephone interview concerning the opportunities and limitations of job applications by people with epilepsy in Austria. The interviews were performed in May 2020 in the district of Salzburg, Austria, among companies with at least 10 milllion Euro transaction volume. The interviews were analyzed by the qualitative method of content analysis (Kuckartz). The legal situation was also analyzed.
Results: Employers were confident that employees with epilepsy can be managemed well in case a value system and first responders are in place. The Austrian legislation predisposes to uncertainty with both employers and employees. In particular, the Austrian law permits only

retrospective juridical clarification. The authors developed a classification system for work places with “D-0” meaning no health or financial danger (e.g. office workers), “D-1” poses still no health hazard but includes regular work with cash (e.g. salespersons), and “D-2” with potential medical implications for the person with epilepsy or any other person at the workplace (e.g. industrial worker). With D2, occupational health practitioners evaluate the applicant`s medical fitness for the job without disclosing medical details. We designed a “compartment-model of medical information in the application process” to guarantee that the occupational physician is the only person who learns about the applicant`s medical details.
Conclusion: The practical and simple classification of workplaces and concept for keeping medical information confident may result in diminishing enacted and felt stigma in the working world for people with epilepsy and also for all other diseases.

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Anti N-methyl-D-aspartate receptor (NMDAr) encephalitis during pregnancy: a case report and a narrative review of the literature

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Purpose: The anti-N-methyl-D-aspartate receptor (NMDAr) antibodies encephalitis is the most frequent autoimmune encephalitis (AE) occurring in young women. Few cases of anti-NMDAR encephalitis during pregnancy have been described. In treating this condition, the clinician must consider the teratogenic and toxic effects of treatments on the fetus. This study aims to describe a case of an anti-NMDAR AE during the first trimester of pregnancy and reassume the available data in the literature about the therapeutic management of AE during pregnancy.
Method: A 29-year-old woman in the 7th gestational week came to our observation for the sudden onset of continuous, ongoing, focal motor seizures involving the right side of the face. The patient underwent a video-EEG recording, which showed continuous high-amplitude rhythmic 5 Hz slow waves and sporadic diphasic sharp waves over the left fronto-centro-temporal derivations. MRI scans showed hyperintense alterations over the left temporal-frontoparietal cortex in FLAIR T2-weighted sequences. A lumbar puncture showed lymphocytic pleocytosis with increased protein and positivity for anti-NMDAR antibodies. A diagnosis of anti-NMDA AE was made. The patient was treated with anti-seizure medication and immunotherapy (steroids and plasmapheresis) with a progressive improvement of the clinical picture. The fetal ultrasound (FU) showed standard biparietal and cerebellar indices, normal abdomen dimension, and heart kinetic.
Results: Treatment of anti-NMDAR AE during pregnancy is challenging. In treating this condition, a combined ASM and immunomodulant therapy are usually needed. According to the literature, both plasmapheresis and corticosteroid treatment show a better safety profile

than Rituximab. In patients with bilateral tonic-clonic seizures, sodium channel blockers seem to be more effective in seizure control.
Conclusion: Even though no randomized trials or large-cohort observational studies are available, our report and the literature evidence support immunomodulatory treatment with systemic steroids and PLEX and ASM treatment with sodium channel blockers as the best approach in anti-NMDAR AE management during pregnancy.

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Challenging diagnosis of familial adult myoclonic epilepsy presenting as a progressive myoclonic epilepsy

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Purpose: The aim of this clinical report is to expand the clinical spectrum of familial myoclonic epilepsy (FAME), typically regarded as a benign condition, to include a severe phenotype of progressive myoclonic epilepsy (PME: myoclonus, epilepsy and neurological progressive deterioration). Since FAME is caused by intronic repeat expansions, which are not detected by current NGS-techniques employed in routine practice, a clinical diagnosis is mandatory to guide the appropriate genetic testing.
Method: Description of the clinical and genetic diagnostic approach of a FAME family presenting with a PME phenotype.
Results: The proband is a 41-yo female who presented with a first TC bilateral seizure in November 2021. She had a previous history of upper limbs tremor and walk difficulties that have progressively worsened since the third decade of life. Clinical examination revealed myoclonus, ataxia, dysarthria and nystagmus. A video-EEG study showed frequent generalized spike-wake discharges, myoclonic seizures and myoclonus without an EEG correlate, but jerk-locked averaging was not performed. SEPs were normal and brain MRI revealed a marked atrophy of cerebellum. His 71-yo father presented at age 27 with the same clinical picture. He has been wheelchair bounded since age 60. Nor the proband or his father suffer cognitive impairment. A sequential exome approach analyzing pathogenic variants in genes related to spinocerebellar ataxias and PMEs was done. The negative results lead us to evaluate the possibility for the clinical picture of this family to be a rare presentation of FAME. An intronic repeat (TTTTA/TTTCA) expansion in MARCH6 was confirmed by means of repeat-primed PCR.
Conclusion: The clinical spectrum of FAME may include a severe phenotype presenting as a PME. Thus, FAME and repeat expansions should be considered among the differential diagnosis and potential genetic cause of the autosomal dominant PMEs that have remained negative to genetic testing so far.

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Heart rate variability modifications in adult patients with early versus late-onset

temporal lobe epilepsy: a comparative observational study

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Purpose: Temporal lobe epilepsy (TLE) is the most frequent form of focal epilepsy. TLE is associated with cardio-autonomic dysfunctions and increased cardiovascular (CV) risk in patients over the fifth decade of age. In these subjects, TLE can be classified as early-onset (EOTLE; i.e., patients who had developed epilepsy in their youth) and late-onset (LOTLE; i.e., patients who developed epilepsy in adulthood). The heart rate variability (HRV) analysis is useful for assessing cardio-autonomic function and identifying patients with increased CV risk. This study compared changes in HRV occurring in patients (older than 50) with EOTLE or LOTLE.
Method: We enrolled twenty-seven adults with LOTLE (LOTLE group) and 23 EOTLE (EOTLE group). Each patient underwent a EEG + EKG recording during 20-minutes of resting state and a 5-minutes hyperpnea (HP). Short-term HRV analysis was performed both in time and frequency domains. Linear Mixed Models (LMM) were used to analyze HRV parameters according to the condition (baseline and HP) and group (LOTLE and EOTLE groups).
Results: Compared to LOTLE group, the EOTLE group showed significantly decreased Ln-RMSSD (natural logarithm of the root mean square of the difference between contiguous RR intervals) (p-value=0.05), LnHF ms^2 (natural logarithm of high frequency absolute power) (p-value=0.05), HF n.u. (high frequency power expressed in normalized units) (p-value=0.008) and HF% (high frequency power expressed in percentage) (p-value=0.01). In addition, EOTLE patients exhibited increased LF n.u. (low frequency power expressed in normalized units) (p-value=0.008) and LF/HF (low frequency/high frequency) ratio (p-value=0.007). During HP, the LOTLE group exhibited a multiplicative effect for the interaction between group and condition with increased LF n.u. (p=0.003) and LF% (low frequency expressed in percentage) (p=0.05) values.
Conclusion: EOTLE is associated with reduced vagal tone compared to LOTLE. Patients with EOTLE may have a higher risk of developing cardiac dysfunctions or cardiac arrhythmia than LOTLE patients.

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Tau neuropathology identified following surgery to control seizures in patients with drug resistant epilepsy (DRE)

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Purpose: Tau protein plays a major role in the pathogenesis of many neurodegenerative

diseases especially Alzheimer Disease and Chronic Traumatic Encephalopathy (CTE). More than 50% of individuals with epilepsy will develop neurodegenerative, neurocognitive and/or neuropsychiatric comorbidities. Prior studies have suggested a link between epilepsy and tau pathology. We studied a cohort of individuals with Drug Resistant Epilepsy (DRE) who underwent resective epilepsy surgery at the Irish National Epilepsy Centre from 2016 to 2020 in order to determine the prevalence of Tau pathology in patients with DRE.
Method: Available neuropathology specimens were examined in 23 patients who underwent resective epilepsy surgery between 2016 and 2020. All specimens were re-examined for Tau pathology and assessed independently by two neuropathologists unaware of the patients clinical status. Comparison was made between patient's age at surgery, epilepsy duration, ILAE classification together with pre-surgical neuropsychology profiles and structural brain imaging between Tau Positive and Tau Negative patient groups.
Results: Of the 23 patients whose resected brain tissue was available for re-examination, nine patients had Tau positive immunohistochemistry. Ages of patients staining positive ranged between 25 and 54 at the time of surgery, seven of whom were aged 40 or less. Of those, four patients had cavum septum pellucidum (CSP) on MRI brain. The relationship between CSP and tau positivity was found not to be statistically significant ($X^2 = 0.608$, $p = 0.435$).
Conclusion: In the small number of resective surgical specimens examined, 9/23 stained positive for tau immunohistochemistry. The majority of patients staining positive for tau were under the age of 40. While the correlation between CSP and duration of epilepsy was not statistically significant, our findings suggest that tau pathology may be present in the brains of epilepsy patients at markedly younger ages than previously predicted. These findings suggest further study into this area is warranted.

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Epilepsy and cognition – a bidirectional relationship

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Purpose: Epileptic activity may cause impairment of cognitive function, immediate during epileptic discharges by disruption of essential neuronal processes for cognition, and/or in the long-term by lasting damage of important structures or alteration of synaptic connections. Less known is the reverse, that attention and full cognitive presence can improve or inhibit epileptic activity. The aim of this presentation is to describe and elucidate aspects of this bidirectional relationship by real-life examples.
Method: 69 patients from a hospital-based neurology practice with integrative medicine care were reviewed. Medical records were screened for the results of EEG including long-term monitoring, for results of cranial MRI, for cognitive testing, and for current anticonvulsant treatment, including cannabidiol and/or progesterone. For each patient, expert clinical opinion of the treating epileptologist was obtained for any interactions between epileptic activity

and cognition, between anticonvulsants and cognition, and between structural deficits and epileptic activity and/or cognition.
Results: Nine different types of interaction were identified (labeled A-I).
Effects of cognition on epileptic activity: A. Cognitive self-control can reduce epileptic activity (20/69 patients or 29%). B. Attention deficit or cognitive impairment can increase epileptic activity (22%).
Effects of epileptic activity on cognition: C. Attention deficit as result of epileptic activity (28%), D. Impairment of memory deficit as result of longstanding epileptic seizures (16%).
Effects of anticonvulsive medication on cognition: E. Cognitive improvement (13%), F. Attention impairment (41%), G. Memory impairment (24%).
Effects of cerebral defects: H. Causing epilepsy (43%), I. Causing cognitive impairment (37%).
Conclusion: Awareness of the anticonvulsant effects of attention and mental presence can improve seizure control and patient well-being by the practice of self-control techniques, lifestyle management and optimal choice of antiepileptic medication. These measures may even reduce the required dosage and limit cognitive and other undesired side effects and should be part of optimal care for all epilepsy patients.

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Localization, type, and size of stroke possible risk factors for developing poststroke epilepsy

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Purpose: The aims of the study were to determine: the frequency of PSE in the group of examinees, the
the difference in the frequency of PSE in ischemic stroke and intracerebral hemorrhage (ICH) group, the influence of the size and location of the lesion, on the occurrence of PSE
Method: Material and methods: This prospective study analyzed patients with the first stroke of ischemic
and hemorrhagic genesis, with a follow-up period of two years
Results: Results: A number of 267 patients (aged 47-92) who had the first stroke, were analyzed. In the control group (n=246) after the stroke, PSE did not develop and the other group
(n=21) included patients who had PSE. Cortical and subcortical lesions had a statistically significant ($p < 0.05$) influence on the development of epileptic seizures after the stroke. A statistical significance between the size of the lesion, as well as the type of stroke and PSE, was not
determined.
Conclusion: Conclusions: The frequency of PSE in the examined group was 7.86%.
Cortical and subcortical lesions were shown to be statistically significant for the occurrence of PSE. The significance of ICH and the size of the lesion for the onset of PSE has been described in the

literature, but we have not found statistical significance regarding their impact on PSE occurrence in our experimental group of patients.

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Reflex focal epilepsy provoked by memory retrieval: a StereoEEG case report

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Purpose: We report a unique case of a 25-year-old right-handed female with cerebral palsy and refractory epilepsy with a reflex component studied with stereoEEG
Method: The pateint gave the description of her seizures as a feeling of déjà vu. Interestingly she reported being able to trigger her seizures by retrieval of specific memories from her childhood. She felt like she was sinking deeper into the memory and losing contact with her environment followed by some autonomic signs, swallowing motions and subtle twitches of her right nasolabial fold. She denies generalized seizures or status epilepticus. After a trial of at least 3 anti-epileptic medications, she was deemed refractory and a surgical candidate. Scalp EEG showed right temporal interictal discharges and typical seizures captured showed an ictal onset in the right temporal region with an evolving delta rhythm.
Her MRI showed a subtle right amygdalar enlargement without alterations in architecture. PET scan showed reduced metabolism in the right temporal lobe. A Magnetoencephalogram showed posterior temporal dipoles. Due to prominent autonomic features in the semiology, the relatively atypical EEG morphology and the lack of clear lesion on MRI it was decided to implant her with stereo- EEG to further localize her epilepsy.
Results: Several spontaneous seizures were captured on SEEG with typical semiology and were seen to be arising from the amgydala followed shortly by the hippocampus and parahippocampal gyrus. The most unique phenomenon however was the ability to confirm the reflex component of her epilepsy. We asked her to retrieve her childhood memories known to provoke seizures. In seconds the intracranial EEG showed onset of a seizure with a typical electrographic pattern arising from the amygdala. This experiment was repeated a couple of times to prove reproducibility.
Conclusion: This is an original stereoEEG recording of a reflex focal epilepsy

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Epilepsy related complications during COVID-19 wave in China: data from a three-center prospective cohort in China

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Purpose: To investigate the epilepsy-related complications of COVID-19 during the first Omicron wave in China
Method: In this three-center cohort, we prospectively reviewed patients admitted to the neurological ward during 12 December to 12 January. Data were extracted from medical records through a designed case report form. Demographics and clinical data were obtained and analyzed. Data from last year when none of the in-patients were infected were also collected as control cohort.
Results: We enrolled 790 patients, among whom 436 were infected with COVID-19. There is no significant difference in age, gender, COVID infection history, and length of stay among the three centers. The ward treated 92 patients with epilepsy during the study period, of whom 10 patients complained the worsen or relapsed of their well-controlled seizure. Five patients experience their first lifetime seizure and considered newly diagnosed epilepsy after exclusion of other acute etiology. Although the number of patients with epilepsy did not change significantly compared to last year, the number of encephalitis ($P<0.00$) and encephalopathy ($P<0.00$) have sharply increased. In 79 patients diagnosed with encephalitis, 14 of them have seizure as their chief complaints. Among those who were indicated with lumbar puncture, we randomly tested 48 CSF sample with PCR test and find 34 of them showed positive results.
Conclusion: Our data revealed the disease shift during the epidemic of COVID-19 wave in China. When other selective admission were delayed, the ratio of newly onset seizure and encephalitis have significantly increased. Although the CSF results suggested there could be possible neurological insult during COVID-19 infection. Whether it will indirect or indirectly cause encephalitis and encephalopathy would still need more robust evidence.

Basic science

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Proteomics analysis of synaptosomes of brain tissue from patients with pharmacoresistant mesial temporal lobe epilepsy

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Purpose: The study of synaptosomes can give clues about synaptic transmission and its abnormalities since they contain all the machinery involved in releasing, reuptake, and storing

neurotransmitters. In addition, synaptic proteins may be therapeutic targets in many neurological diseases. Mesial temporal lobe epilepsy (MTLE) is the most common type of focal epilepsy in adults, with a high proportion of patients who do not respond to treatment with antiseizure medication. This study aims to characterize the proteome of synaptosomes isolated from the tissue of patients with pharmacoresistant MTLE.
Method: We analyzed the synaptosomes from brain tissue obtained from epilepsy surgery (hippocampus and anterior temporal lobe) of patients with pharmacoresistant MTLE (N=20 – 5 per group) and compared these with *post-mortem* control tissue (N=5). We classified the patients into four groups according to disease duration determined at the time of epilepsy surgery, 10, 20, 30, and 40 years. We isolated the synaptosomes, and proteomic data were acquired using an Orbitrap Eclipse™ Tribrid™ (MacDonald Laboratory – University of Pittsburgh). *We used the* ProteomeDiscoverer and R software for bioinformatics analysis. We also performed a SynGO analysis to evaluate the identified biological classes of proteins.
Results: Overall, we identified 1,890 proteins and 7,521 peptides. We found differences in the protein content of the synaptosome of the four groups of patients. A preliminary analysis showed that most proteins identified in the synaptosome of patients belong to the presynaptic fraction, followed by the post-synaptic and the synaptic membrane.
Conclusion: Our study explores for the first time the protein content of the synaptosome in the brain tissue of patients with pharmacoresistant MTLE. As an initial finding, we identified differences in the proteomic content of these vesicles according to the duration of epilepsy. In addition, we expect to identify novel proteins that may play a role in disease mechanisms and pharmacoresistance.

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Pathological paroxysmal slow wave events as a predictive and diagnostic biomarker of post-traumatic epilepsy

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Purpose: Post-traumatic epilepsy (PTE) is a form of acquired epilepsy that results from traumatic brain injury (TBI). We recently showed that transient shifts in the cortical network activity, termed paroxysmal slow wave events (PSWEs) have promising potential as a predictive biomarker for epilepsy in human patients following a first seizure (Zelig, 2021). PSWEs were defined as abrupt slowing of cortical network activity (in rodents <5Hz lasting for >6 seconds; Milikovsky, 2019). We hypothesized that PSWEs reflect network re-wiring during epileptogenesis and therefore can aid in identifying TBI patients at risk of developing post-traumatic epilepsy. The aim of the current study was to examine the potential of PSWE quantification as

a biomarker for post-traumatic epilepsy (PTE) in rodent models of closed-head injury.
Method: We developed two rodent models of close-head brain injury that recapitulated the neurological and cognitive characteristics of mild and moderate TBI in human patients. We implanted epidural electrodes to record spontaneous brain activity up to 9 months post TBI. A sham (no-hit) group was included in the study.
Results: Moderate TBI animals had a significantly higher mortality rate (34%) compared to mild TBI rats ($p<0.05$). TBI rats had longer righting times ($p<0.0001$), BBBD ($n=16$, $p<0.05$), and poor neurological and cognitive outcomes compared to sham ($p<0.005$, $p<0.05$, respectively). Seizure-like events (SLEs) were recorded in 40% of mild and 57% of moderate TBI rats. SLEs had a significantly higher occurrence in TBI animals compared to sham ($p<0.005$). Animals with SLEs had a higher number of PSWEs per hour and spent more time in slow events than animals with no detected SLEs ($p<0.05$).
Conclusion: The occurrence of PSWEs is associated with the development of PTE in two rat models of closed brain injury.

Funding: CIHR Grant no. 148896

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Early evidence of the potential role of HMGB1 in post-traumatic epilepsy and cognitive impairment

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Purpose: Traumatic brain injury (TBI) is a prevalent cause of morbidity and mortality worldwide and is correlated with a high susceptibility to developing posttraumatic epilepsy (PTE) and cognitive dysfunction. High-mobility group box 1 (HMGB1) is a novel inflammatory mediator implicated in the pathogenesis of TBI and PTE. We aimed to investigate the potential role of HMGB1 in PTE and how it leads to cognitive impairment in TBI patients.
Method: This prospective observational longitudinal study was conducted at University Kebangsaan Malaysia Medical Centre (UKMMC), a teaching hospital in Kuala Lumpur, Malaysia. Sixty TBI patients were followed up at three-time points; during admission, at six months, and 12 months post-TBI. HMBG1 levels were sampled from the blood during each visit and analysed using the ELISA technique. Seizure type and frequency were evaluated with standard clinical assessment. Cognitive assessments were administered at six months and 12 months visit using Addenbrooke's Cognitive Examination-III (ACE-III), Wechsler Adult Intelligence Scale 4th Edition (WAIS-IV) subtests: Symbol search and coding and Comprehensive Trail Making

Test (CTMT).
Results: Our findings revealed a significant association between elevated levels of HMGB1 and the development of PTE and cognitive dysfunction in TBI patients ($p<0.05$), providing robust evidence for a potential causal link between HMGB1 and the long-term complications of TBI. This study expanded upon previous research implicating HMGB1 in the aetiology of TBI and PTE, providing valuable insights into these debilitating complications' underlying mechanisms.
Conclusion: In conclusion, our study supplied preliminary but crucial evidence for the involvement of HMGB1 in the development PTE and cognitive impairment in TBI patients. This could be a foundation for further research to investigate the underlying mechanism of HMGB1 in TBI. There is a potential for targeting HMGB1 as a therapeutic strategy for preventing or alleviating these complications.

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Sigma-1 as a target for antiseizure and disease-modifying effects? Impact of a positive modulator on kindling acquisition

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Purpose: Sigma-1 is an atypical receptor protein that can affect mitochondrial function and activity of several voltage-gated ion channels and neurotransmitter receptors. Because of its important role in controlling homeostasis, Sigma1 might be an interesting target for disease-modifying and preventive approaches. Building on previous findings, we addressed the hypothesis that E1R, a positive allosteric modulator of Sigma-1, might exert disease-modifying effects with an impact on progression in an amygdala kindling paradigm.
Method: Female NMRI mice were kindled by once daily suprathreshold stimulations via a depth electrode in the amygdala. Following pre-kindling threshold analysis, animals were randomly allocated to different treatment groups receiving intraperitoneal injections of vehicle, E1R (50 or 75 mg/kg) or the Sigma-1 antagonist NE100 (35 mg/kg) prior to the stimulations. Kindling progression was evaluated with an analysis of seizure severity as well as seizure and afterdischarge duration.
Results: First data provide evidence that E1R exerts relevant effects on kindling progression with a delay in the generation of generalized seizures. Moreover, the kindling-associated progressive increase of motor and electrographic seizure duration was slowed in E1R-treated mice. In contrast, the progression of seizure severity and duration in animals exposed to NE100 proved to be comparable to that in vehicle-treated mice. Following a washout phase, animals were re-stimulated to evaluate a possible longer lasting effect. Generalized seizures

were observed in animals from all groups during the re-stimulation phase.
Conclusion: The findings indicate an impact of positive Sigma1 modulation on the generation of a hyperexcitable kindled network. These data further confirm that Sigma-1 is a target of interest for epilepsy management. Further studies are ongoing to assess a possible disease-modifying and preventive effect in a model with spontaneous recurrent seizures.
Acknowledgements: Funded by DFG PO 681/12-1. Technical support by Victoria Stocker and Cristina Monio Baca. E1R provided by LIOS.

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Interictal electrographic activity in a model of epilepsy based on focal cortical dysplasia type II

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Purpose: Focal cortical dysplasia (FCD) is a localized, highly epileptogenic malformation of the cerebral cortex that is a common cause of pharmacoresistant epilepsy. Pathological high-frequency oscillations (pHFOs) are considered as a marker of seizure onset zone, but the mechanisms behind them are not well understood. In this study, we aimed to describe interictal electrographic activity in a chronic FCD model.
Method: FCD was induced by in utero electroporation (n=8) of the mTOR mutation p.Leu-2427Pro found in human focal cortical dysplasia type IIb. At the age of 8-10 weeks, animals were implanted both in the FCD and nonlesional regions and video-EEG monitored for a minimum of 14 days. After the manual removal of artifacts, the EEG was subjected to interictal epileptiform discharge (IED) detection by the method of statistical envelope distribution estimation. Pathological oscillations were detected in both gamma-ripple (pGRO, 45-250 Hz) and fast-ripple (pFRO, 300-800 Hz) bands by the method of energy envelope thresholding.
Results: FCD animals displayed a significantly higher pFRO rate (0.05 ± 0.16 events/min) compared to control animals (0.0016 ± 0.0012 events/min ; SEM; $p<0.01$, Wilcoxon test). pGRO rate was higher in FCD animals (0.011 ± 0.031 events/min) compared to control animals (0.00016 ± 0.00011 ; SEM; $p<0.05$, Wilcoxon test). There was no significant difference in IED rate. Within the FCD animals, both pGRO and pFRO rates were significantly higher in the lesion compared to the area outside the lesion ($p<0.05$, Wilcoxon test). The frequency of pGRO oscillations was increased in the lesion compared to the area outside the lesion ($p<0.05$, Wilcoxon test).
Conclusion: We demonstrated that FCD generates a spectrum of HFOs ranging from gamma-ripple oscillations (pGRO) to fast-ripple oscillations (pFRO). The study confirmed the high-

er specificity of pHFOs in epileptogenic lesion localization compared to traditional IEDs. Understanding the functional organization of FCD is crucial for improving the surgical treatment of the patients.

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Voluntary aerobic running activity improves pathologic outcomes in a mouse model of acquired epilepsy

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Purpose: Healthy life-style may improve neurological outcomes after acute brain injuries. In particular, physical activity was suggested to reduce neurological deficits and seizures in epilepsy. We investigated if aerobic regular running activity affected epilepsy incidence, seizures burden and neuropathology following an epileptogenic brain injury in mice.
Method: C57BL6/N adult male mice had free access to running wheels in their home cage for 5-weeks before intra-amygdala injection of kainate to induce status epilepticus (SE), followed by epilepsy development (Cohort 1). After SE, Cohort 1 mice were allowed to run for additional 6-weeks, followed by 2-weeks (24/7) ECoG monitoring to quantify spontaneous seizures. Cohort 2 mice were allowed to run for 6-weeks starting 24h post-SE, then ECoG monitored for 2-weeks. Control sedentary mice were injected with kainate but left in their home cage without running wheels. Sham mice were saline-injected and used for histology.
Results: Cohort 1 mice displayed shorter SE duration and reduced cumulative number of spikes vs sedentary mice ($p<0.05$). Epilepsy incidence was reduced by half but number of seizures/2-weeks was similar to sedentary mice. However, average seizure duration was significantly shorter in running mice ($p<0.05$) and this was associated with rescue of hilar GluR2/3 -positive mossy cells. Seizure duration negatively correlated with the number of hilar mossy cells ($p<0.05$). The increase in hilar doublecortin-positive cells (aberrant neurogenesis) and hippocampal BBB damage in sedentary epileptic mice were both reduced in running mice ($p<0.05$). In cohort 2 mice, epilepsy incidence was reduced by 2.5-times ($p<0.05$), the cumulative and average number of seizures/2-weeks were reduced ($p<0.05$) but not their duration, and hilar mossy cells were not rescued vs sedentary mice. Hippocampal pyramidal neuron loss was not affected in both animal cohorts.
Conclusion: Voluntary aerobic physical activity improved pathologic outcomes after an epileptogenic brain lesion. Physical exercise has disease modifying effects which depend on running experience.

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Chemically-induced acute epileptic seizures in zebrafish: a systematic review

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Purpose: The use of zebrafish as a model organism is gaining evidence in the field of epilepsy as it may help to understand the mechanisms and behavioural alterations during epileptic seizures and to discover new therapeutic targets. As zebrafish assays became popular, heterogeneity between protocols increased, leading to conflicting findings. We conducted a systematic review to comprehensively profile the zebrafish acute seizure models.
Method: Literature searches were performed in PubMed, Scopus, and Web of Science, followed by a two-step screening process based on inclusion/exclusion criteria. Qualitative data was extracted and a sample of 100 studies (49.5%) was randomly chosen for risk of bias assessment.
Results: Out of the 1058 studies identified after removing duplicates, 202 met the inclusion criteria. The most common chemoconvulsants were pentylenetetrazole (n=181), kainic acid (n=10), and pilocarpine (n=7). Main outcomes assessed were seizure scores and locomotion. Drugs significantly increased seizure severity and locomotor activity in a dose-dependent manner. Significant variability was also found in key measures such as administration route, duration of exposure, and dose/concentration. Experiments were mostly conducted with larvae (n=133), followed by adults (n=71), embryos (n=6), and juveniles (n=3). About 94% of the studies were rated as low risk of bias for selective reporting, 67% for baseline characteristics of the animals, and 54% for blinding. Randomization procedures and incomplete data were rated as unclear in 81% and 68% of the studies respectively. Sample size calculation was not reported in any of the studies.
Conclusion: Our literature synthesis revealed significant methodological heterogeneity and reporting problems, hindering the estimation of the internal validity of this set of studies. In spite of that, our study offers a comprehensive guide on interventions and outcomes of interest for future epilepsy research using zebrafish.

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Combining TSPO PET and magnetic resonance spectroscopy to measure neuroinflammation in a rat model of traumatic brain injury

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Purpose: There is considerable emerging evidence for the role of neuroinflammation in the development of epilepsy following traumatic brain injury (TBI). We measured brain inflammation longitudinally by in-vivo imaging techniques, Positron Emission Tomography (PET) imaging of translocator protein (TSPO) and Magnetic Resonance Spectroscopy (MRS) for evaluation of brain neuroinflammatory metabolites such as myoinositol, in a rat model of TBI to determine the potential of in-vivo measures of neuroinflammation as predictive biomarkers for post-traumatic epilepsy and other long-term neurobehavioral consequences.
Method: TBI was induced by fluid percussion injury in SD rats. At 1-week and 1-month time points post-TBI, the brain TSPO levels were measured by PET imaging after intravenous injection of the radiotracer ([^{18}F]-FBR) followed by 60 min static PET acquisition and a 5 min CT scan for attenuation correction. Using a PRESS sequence, the levels of brain metabolites such as myoinositol were measured by 9.4T magnetic resonance spectroscopy (MRS).
Results: A significant up regulation of TSPO binding was observed in the ipsilateral cortex of TBI rats compared to sham rats at 1-week post-TBI (n=30, p=0.0007) and remained elevated at 1-month (p=0.009). Enhanced TSPO binding was also observed in the hippocampus at 1-week (p=0.0137) and 1-month (p=0.012) and in the thalamus at 1-week (p=0.0054) and 1-month (p=0.0007) timepoint. Myoinositol level was significantly elevated in the perilesional cortex (p=0.0005) and hippocampus (p=0.04) at 1-month post-TBI as well as in the thalamus at 1-week (p=0.04) and 1-month (p=0.002) timepoint. A positive correlation was observe between the TSPO and MI levels in different brain regions.
Conclusion: TSPO expression and myoinositol levels, assessed using in-vivo PET and MRS, were increased in brain regions relevant to epilepsy and behavioural impairments at 1-week and 1-month post-TBI, indicating microglial proliferation and enhanced neuroinflammation. Imaging inflammation by these techniques should be explored as a potential predictive biomarker for epilepsy and neuro-behavioural outcomes post-TBI.

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Exploring the landscape of epilepsy biomarker research: a bibliometric analysis from 1935 to 2022

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Purpose: Biomarkers are measurable indicators of a biological state or process that can be used to diagnose or predict the risk of disease. In recent years, there has been an increased interest in identifying biomarkers for epilepsy that can be used for early diagnosis, prognosis, and treatment monitoring. We aimed to understand the current state of research in epilepsy biomarkers and identify critical trends using bibliometric analysis

Method: We analysed a dataset of 602 articles published from inception to August 2022 in the Scopus database. We used various bibliometric indicators such as citation count, h-index, and analysis of citation metrics using Herzing's Publish or Perish to identify the field's most influential journals, authors, and research themes. VOSviewer software was used to visualise the data.
Results: Our results show that epilepsy biomarkers research has grown significantly over the past 20 years, with a steady increase in publications. The most influential journals in the field are *Epilepsia* and *Epilepsy and Behavior*. The most prolific authors are Vezzani A., Teresa T., and Surges R. The four most prominent research themes include 'neuroinflammation', 'neuropsychiatry and therapy', 'diagnostics', and 'epileptogenesis and advanced technology'.
Most of the articles were published in the United States and Europe, with the most active countries being the United States, China, and the United Kingdom. The most productive institutions were The UCL Queen Square Institute of Neurology, followed by the University of California, Los Angeles. The analysis of keywords revealed that EEG, IL-1, microRNA, IL-6, IL-10, TNF, and HMGB1 gained the highest attention in later years. Our analysis showed that genetics and advanced technology appeared to be among the future hotspots for research.
Conclusion: Overall, this bibliometric analysis provides a comprehensive overview of the current state of epilepsy biomarker research and highlights key trends and opportunities for future research.

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Intracerebroventricular or intraparenchymal administration of orexin type-2 receptor agonist on spike-and-wave discharges of genetic absence epilepsy rats

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Purpose: Orexin is a neurotransmitter that plays an important role in the circadian rhythm, specifically sleep-wake system, and binds to orexin-1 and orexin-2 receptors in brain. YNT-185, a non-peptide orexin-2 receptor agonist, has been investigated in sleep-arousal network and disorders related to the sleep architecture. In this study, we examined the effect of YNT-185 injection into the right lateral ventricle (ICV) or the ventro-basal nucleus of the thalamus (VB) or the somatosensory cortex (S1) on spike-and-wave discharges (SWDs) of genetic absence epilepsy rats from Strasbourg (GAERS).
Method: Under isoflurane anesthesia, we stereotaxically inserted unilateral ICV or bilateral

VB or bilateral S1 guide-cannulas and electroencephalography (EEG) recording electrodes on the skull of 200–350g male GAERS. After one-week-recovery, 3-hour basal EEG recordings were obtained from animals. The following day, the doses of YNT-185 were administered via guide-cannulas: 100-nmol/10uL (n=9), 300-nmol/10uL (n=8) or 600-nmol/10uL (n=7) for ICV group; 30-nmol/500nL (n=3), 40-nmol/500nL (n=5) or 60-nmol/500nL (n=3) for VB group; 40-nmol/500nL (n=6) for S1 group. EEG signals were recorded using Powerlab-8S system and thereafter analyzed with the LabChart-8.0. For statistical analysis, one-way Anova was used ($p<0.05$ was considered significant).

Results: The ICV injections of YNT-185 dose-dependently decreased the cumulative duration of SWDs when compared to baseline recordings of GAERS ($p<0.05$). However, intraparenchymal administration of YNT-185 into the VB or S1 produced no significant effect on the cumulative duration of SWDs compared to baseline.

Conclusion: The decrease in the SWDs with ICV administration of YNT-185 suggests an orexin-2 receptor-mediated modulation of absence seizure network. However, there is no significant effect by the intraparenchymal VB or S1 injection of YNT-185 on the SWDs in GAERS. In the future studies, we aim to investigate other brain regions responsible for the ICV YNT-185 effect.

Supported by Acibadem University Scientific Research Projects Commission (ABAPKO; 2022/02-26) and GEMSTONE Horizon-Europe (101078981).

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Temporal and spatial correlates of paroxysmal slow wave events in the epileptic brain

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Purpose: Epilepsy can have a wide range of clinical manifestations making it often difficult to diagnose. EEG is a common tool and an essential aid in the diagnosis and management of epilepsy. However, EEG is considered normal in almost 50% of patients with epilepsy. Hence, there is a need for an objective measure that could be used as a diagnostic, prognostic and pharmacodynamic biomarker. Paroxysmal slow wave events (PSWE), a transient slowing of neuronal activity during which median power frequency falls <5Hz for > 10s, have been proposed as a new biomarker for epilepsy. However, the source and relationship between transient network slowing and seizure activity are not known. Our study aimed to bridge this gap of knowledge while using a rat model of temporal lobe epilepsy.

Method: Rats were poisoned using the organophosphate paraoxon leading to status-epilepticus and epileptogenesis. Animals were subsequently implanted using both intracerebral and epidural electrodes. Seizures and interictal epileptiform activity were detected by visual inspection. PSWE detection and data analysis were performed using Matlab "home-made" scripts and PRISM.

Results: PSWEs probability peaked first in the lateral entorhinal cortex (LEC). Correlogram analysis showed a strong and significant temporal correlation between PSWEs and seizure onset. We also found that spike and wave activity in the LEC was synchronized with PSWEs and slowings recorded through epidural electrodes. Correlation of signal filtered in the PSWE range (1-5Hz) increased significantly ($p<0.0001$, $n=10$) between these electrodes during PSWEs.
Conclusion: We found that PSWE strongly correlates with seizure activity and that deep epileptiform activities could correlate with surface recordings of slow waves during PSWEs. Together, these results support the notion of PSWE as a biomarker for epilepsy-related activity.

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The atypical anticonvulsive mechanism of soticlestat characterized in animal models of epilepsy

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Purpose: Over 30% of patients with epilepsy have seizures that are poorly controlled with currently available medications, highlighting the importance of novel therapeutic mechanisms. Soticlestat is a potent, specific inhibitor of cholesterol 24-hydroxylase (CH24H) now in phase 3 clinical trials for treatment of Dravet syndrome and Lennox–Gastaut syndrome. CH24H inhibition is a novel approach that has not been extensively studied to date. Following the identification of its antiepileptic potential in a mouse model of Alzheimer's disease, the anticonvulsive properties of soticlestat were studied in rodent models of epilepsy that are commonly used to characterize antiseizure medications.
Method: We assessed the efficacy of soticlestat in the mouse maximal electroshock seizure, pentylenetetrazol and 6Hz psychomotor acute seizure mouse models, the Frings audiogenic seizure-susceptible (AGS) mouse, the rat amygdala kindling, and mouse PTZ and corneal kindling and corneal kindling models of network hyperexcitability and chronic seizures.
Results: Soticlestat was effective in the Frings AGS and kindling acquisition models but not in the other seizure and epilepsy models evaluated. Soticlestat shortened the time of tonic-extension seizures in Fring's AGS mice in a dose-dependent manner with no impact on wild running behaviours. Interestingly, soticlestat retarded amygdala kindling acquisition without altering after-discharge duration. Soticlestat did not suppress already established kindled seizures. These findings suggest that soticlestat can attenuate seizures through a mechanism distinct from conventional antiseizure medications. We propose that soticlestat's unique mechanism of action can modify the course of secondary seizure generalization through a reduction of brain 24S-hydroxycholesterol, which is implicated in pathological mechanisms relevant to seizure generation in epilepsy.
Conclusion: With a unique seizure control mechanism, soticlestat belongs to a potentially

novel class of antiseizure medications and may be a promising therapeutic option for intractable developmental and epileptic encephalopathies such as Dravet syndrome and Lennox-Gastaut syndrome.

Study funded by Takeda Pharmaceutical Company Limited.

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Cortical spreading depolarization causes mitochondrial and vascular dysfunction and is linked with Post-traumatic epilepsy

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Purpose: Traumatic brain injury (TBI) results from an external force to the head, which can lead to early symptoms, such as loss of consciousness, as well as delayed brain disorders including post-traumatic epilepsy (PTE). Understanding the acute pathology after a head impact is therefore key in predicting and preventing long-term outcome. We previously showed that cortical spreading depolarization (CSD) is the earliest electrophysiological event occurring within minutes in ca. 50% of animals exposed to closed head injury. CSD is associated with depolarization of a large population of cells, and depression of neuronal firing.
Method: To study the contribution of CSD on TBI outcome, we electrically triggered CSD in deeply anesthetized rats using the open cranial window approach. We measured cortical blood flow, oxygen pressure and mitochondrial function using laser doppler flowmetry, oxygen sensitive probes and fluorescent dyes. Mitochondrial calcium influx was inhibited by topical application of Ru360. Histopathological *postmortem* analysis included electron microscopy and immunohistochemistry. In other cohorts of animals, we used a closed head weight drop TBI model and animals were implanted with electrocorticography (ECoG) electrodes. Brain activity was recorded at 6-9 months after TBI.
Results: We measured a persistent increase in reactive oxygen species in juxtavascular cells after repetitive CSDs. Inhibition of mitochondrial calcium influx worsened CSD-induced reduction of blood flow and available oxygen. We also detected morphological changes of cortical vasculature, pericytes and mitochondrial cristae damage after triggered CSD or after TBI. Righting latency after triggered CSD was significantly longer compared to sham surgery controls, while longer righting latency after TBI was associated with a higher risk to develop PTE.
Conclusion: Together, we provide evidence that the occurrence of CSD after TBI is associated with damage to brain mitochondria, dysfunctional regulation of cortical blood flow and, in the long term, increases the risk of PTE.

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Impact of zonisamide, tiagabine and pregabalin in an astrocyte-microglia co-culture model of inflammation

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Purpose: Epilepsy is a chronic neurological disorder leading to recurrent epileptic seizures. Treatment with antiseizure medication (ASMs) targeting neuronal structures is the main therapeutic approach. However, there is a strong evidence confirming the involvement of glial cells including astrocytes and microglia in the pathophysiology of epilepsy. Thus, we aimed to investigate effects of different ASMs such as tiagabine (TGB), zonisamide (ZNS) and pregabalin (PGB) in an astrocyte-microglia co-culture model of inflammation.
Method: Primary rat astrocytes co-cultures containing 5-10% (M5, "physiological" conditions) or 30-40% (M30, "pathological inflammatory" conditions) of microglia were treated with different concentrations of ZNS (10, 20, 40, 100 µg/ml), TGB (1, 10, 20, 50 µg/ml) or PGB (3, 10, 30 and 60µg/ml) for 24 h. The glial viability, microglial activation, connexin 43 (Cx43) expression and gap-junctional coupling were investigated.
Results: TGB revealed toxic effects with concentration-dependent reduction of glial cell viability under physiological and pathological conditions. In contrast, ZNS reduced the glial viability only by overdose concentration (100 µg/ml) under physiological conditions. PGB did not affect the glial viability. After incubation of pathological M30 co-cultures with high concentration (20 µg/ml) of TGB, the microglial activation was significantly decreased, suggesting anti-inflammatory features. Otherwise, incubation of physiological and pathological co-cultures with different concentrations of ZNS or PGB resulted in no significant changes of microglial phenotypes. The gap-junctional coupling was significantly decreased after incubation of M5 co-cultures with 20 and 50 µg/ml TGB. A significant decrease of Cx43 expression and disruption of gap-junctional communication were found after incubation of M30 co-cultures with 10 µg/ml ZNS, contributing to anti-seizure activity.
Conclusion: TGB and ZNS revealed different effects on glial features, whereas PGB did not show effects on glia. The astrocyte-microglia co-culture model provides novel perspectives for understanding ASM effects on glia and glia-mediated inflammation and can contribute to exploring novel anti-epileptogenic targets.

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Characterization of vagus nerve electroneurogram (VENG) during acute kainic acid induced seizures

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Purpose: Seizures produce autonomic symptoms, mainly sympathetic but also parasympathetic in origin. Within this context, the vagus nerve (VN) is a key player as it carries information from the different organs to the brain and vice versa. For this reason, exploiting the vagal neural traffic with respect to seizures might offer a novel way to detect seizures and develop a closed-loop Vagus Nerve Stimulation (VNS) system. Therefore, this project aims to develop a Vagus Nerve Electroneurogram (VENG)-based detection algorithm to detect seizures in an acute kainic acid rat (KA) model.
Method: Five male Wistar rats, weighing 275±75g, were used. Anaesthesia was induced using 100mg/kg Ketamine and 7mg/kg Xylazine i.p. and maintained by half concentration of the initial mixture.
Three epidural stainless-steel electrodes were implanted on the frontal cortex ([+]:AP:+2mm, ML:±3mm, [-]:AP:+6mm) to record EEG. Three ECG Lab-made Tungsten electrodes were implanted according to Eindhoven's lead II to record ECG. Finally, a tripolar Micro-Cuff electrode was implanted around the left cervical portion of the VN. Rats were injected with KA (0.4µg/0.2µl saline; 0.1µl/min) in the right hippocampus ([RH]:AP:-5.6mm, ML/DV: 4.5mm) and VENG and EEG were recorded for 20 minutes.
Results: Ten seizures were recorded in 3/5 animals with a mean seizure duration of 52.38±20.98 seconds and a mean delay between the injection and the first seizure of 8.7± 4.34 minutes.
In all seizures, we observed a modification of VN activity characterized by the loss of respiration related rhythmicity in the signal. In addition, in 1/3 rats we observed a clear increase of the envelope of the VENG signal.
Conclusion: Our results show the occurrence of a specific change in VENG activity during acute KA induced seizures in anaesthetic conditions. Therefore, recording of VENG may be useful to detect seizures, which could in the future be used for closed-loop VNS in patients.

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The effect of antiseizure medications and cardioprotective drugs on cardiac injury in a post-status epilepticus rat model of temporal lobe epilepsy

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Purpose: Building clinical and experimental evidence indicates an increased risk of cardiac abnormalities in people with chronic drug-resistant epilepsy. Postulated mechanisms include

cardiac injury from repeated catecholamine surges and hypoxemia, leading to the concept of 'epileptic heart'. This study investigated acute and chronic cardiac injury in a rat model of temporal lobe epilepsy and examined whether early administration of antiseizure medication or cardioprotective drugs can alleviate such injury.
Method: Kainic acid (KA) was used to induce status epilepticus (SE) and subsequent chronic epilepsy in male Wistar rats (n=43). Levetiracetam (200mg/kg/day, n=11), atenolol (5mg/kg/day, n=12), VCP979 – a novel anti-fibrotic and anti-inflammatory agent (7mg/kg/day, n=9), and vehicle (n=11) were administered through an osmotic pump from day 0 to 12 weeks post-SE. Sham rats (n=13) were handled the same way without receiving KA. Blood samples were collected on day 2, day 7 and day 84 post-SE to analyze cardiac troponin I (cTnI) using ELISA. EEG/ECG recordings were performed continuously for 2 weeks between day 70 and day 84 to assess chronic seizure frequency.
Results: Compared to the sham controls, cTnI levels were significantly higher in vehicle-treated post-SE rats at day 7 (227.3 ± 33.5 vs. 127.0 ± 8.8 pg/mL, $p<0.0001$) and day 84 (153.0 ± 7.6 vs. 128.3 ± 8.1 pg/mL, $p=0.0069$). At day 84, there was a positive correlation between cTnI levels and spontaneous seizure frequency ($p=0.0005$, $r^2=0.8721$), and cTnI levels were significantly lower in VCP979- and atenolol-treated groups compared to the vehicle-treated group ($p<0.0001$ and $p=0.0025$, respectively). Overall, the VCP979-treated animals had the lowest cTnI levels during the development of epilepsy, which was similar to the sham controls.
Conclusion: Our findings indicate that acute SE and repeated seizures in chronic epilepsy were associated with cardiac injury, consistent with the 'epileptic heart'. Early treatment with cardioprotective drugs may decrease the risk of seizure-related cardiac injury in this population.

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A role for the slow AMPA receptor in generating epileptiform activity?

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Purpose: Conventional knowledge suggests that fast synaptic excitation mediated by the activation of AMPA receptors (AMPAr) plays a key role in ictogenesis. Recent work has demonstrated the existence of a slow to desensitise AMPAr in cortical pyramidal neurones. The slow AMPAr has a high affinity for glutamate and can remain open for several hundreds of milliseconds (~500 ms). Thus, the presence of this slow AMPAr could bias excitatory neurons towards prolonged pathological depolarisations as observed during ictal activity. We aimed to test for a contribution of slow AMPAr to seizure activity using electrophysiological and pharmacological approaches.
Method: Extracellular local field potential (LFP) recordings were made from acute rodent (entorhinal cortex) and human (neocortex) brain slices (400µm). 4-AP or modified (0.2mM Mg^{2+}/ 8mM K^{+}) artificial cerebrospinal fluid (ACSF) was utilized to induce ictal discharges. Ictal activity was quantified using event duration, first spike amplitude and area power and these

parameters were normalized against the baseline activity of each slice.
Results: In recordings of 4-AP induced ictal activity in the rodent entorhinal cortex, the application of sub-saturating concentrations of the AMPAr antagonist NBQX (300nM) did not significantly alter area power or first spike amplitude. Whilst the duration of ictal events was reduced (N=8; $p<0.05$), overall ictal activity persisted. The subsequent application of a higher concentration of NBQX (1µM) abolished ictal events (N=9). In separate experiments, ictal activity in the presence of sub-saturating concentration of NBQX was abolished by subsequent application of the non-competitive AMPAr antagonist GYKI 52466 (50µM). All parameters were significantly reduced (N=10; $p<0.0001$). In human neocortical slices obtained from patients with refractory epilepsy (N=2) ictal activity was unaltered by sub-saturating concentrations of NBQX but abolished by the higher concentration of the competitive antagonist.
Conclusion: Our preliminary data suggests that slow AMPAr contribute to ictal activity in both rodent tissue and human epileptic tissue.

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Metrics for evaluation of seizure-onset zone localization

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Purpose: In focal drug-resistant epilepsy, precise localization of the epileptogenic zone is a requirement for successful surgical resection. Epileptogenic tissue can be localized using various machine learning models. However, clear guidelines for the evaluation of their performance are not established. We aim to test different classification metrics and recommend an approach suitable for objective model evaluation.
Method: Stereo-electroencephalography recordings from 18 patients with Engel-IA post-surgical outcomes were analyzed. Using a multi-feature approach, channels were classified by a support vector machine as normal or pathologic for three different classification targets (seizure-onset zone (SOZ), resected SOZ and all resected channels). Testing was performed by leave-one-patient-out cross-validation and metrics were: (i) area under receiver operating characteristic (AUROC), (ii) area under precision-recall curve (AUPRC) and (iii) F_β-score.
Results: The ratio of pathologic to normal channels was approximately 1:9 for SOZ, 1:12 for resected SOZ and 1:6 for all resected targets. Considering AUROC, best model performance was achieved for localization of SOZ channels (0.9±0.15 (median±std)), followed by resected SOZ channels (0.88±0.15) and all resected channels (0.84±0.24). Interestingly, model targeting all resected channels achieved the best results for precision-recall metrics (AUPRC = 0.53±0.26, $F_{0.5}$-score = 0.56±0.23, F_1-score = 0.62±0.22 and $F_{2.0}$-score = 0.72±0.21), despite

performing the worst for AUROC. The model localizing resected SOZ channels was ranked second according to AUROC and worst for precision-recall metrics.
Conclusion: We recommend using not only the receiver operating characteristic, but its combination with precision-recall curve and F_β-score. AUROC informs us on the overall diagnostic ability of the model, AUPRC puts focus on accurate localization of pathologic electrodes and F_β-score allows us to specify weights of precision and recall. Sole use of AUROC can be misleading for imbalanced datasets, favoring models with higher ratios of negative cases.

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Investigation of long non-coding RNAs as mediators of aberrant gene expression in temporal lobe epilepsy

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Purpose: Development of temporal lobe epilepsy (TLE) after a precipitating brain insult is associated with large-scale changes in epigenetic-mediated regulation of gene expression, which is a known critical driver for many epileptogenic processes. In contrast to other epigenetic mechanisms, the functional involvement of long non-coding RNAs (lncRNAs) in the pathogenesis of epilepsy remains largely unexplored, although they are increasingly recognized as key modulators of RNA processing at the (post)-transcriptional level. Here, we perform the first comprehensive profiling study of lncRNAs in epilepsy development and progression and assess their utility as novel drug targets.
Method: To study the role of lncRNA dysregulation in TLE, kainic acid-induced post-*Status Epilepticus* mouse models were used. We profiled genome-wide lncRNA expression by performing Next Generation Sequencing on hippocampal brain tissue collected at key timepoints during epilepsy development and applied a stringent bioinformatic filtering approach to predict those dysregulated lncRNAs with the highest pro-epileptogenic potential in the human condition. Using antisense oligonucleotide-mediated lncRNA inhibition we are currently assessing the disease-modifying potential of targeting dysregulated lncRNAs and identifying the underlying mechanisms of action.
Results: Transcriptomic analysis revealed significant changes in numerous lncRNAs strongly influenced by the time after the initial insult. Several of them are known for their importance during embryonic development, in plasticity and cell death, which indicates lncRNA-mediated effects on major epileptogenic disease mechanisms. Based on various characteristics including the expression level, expression change and inter-species conservation, four lncRNAs were selected for ongoing *in vitro* and *in vivo* examination with encouraging preliminary results.
Conclusion: Extensive dysregulation of lncRNA expression during epileptogenesis is a likely contributor to many epileptogenic processes such as synaptic reorganization and cell loss.

This renders lncRNAs promising targets for the development of novel preventive and/or therapeutic treatment approaches.

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Sigma-1 as a target candidate for antiseizure effects: analysis in the mouse amygdala kindling model of temporal lobe epilepsy

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Purpose: Sigma-1 is an interesting target candidate in neurological disorders because of its regulatory function when homeostasis is compromised by pathophysiological mechanisms in disease states. Here, we assessed the antiseizure effects of methylphenylpiracetam (E1R), a selective positive allosteric Sigma-1 modulator. The antiseizure medication fenfluramine appears to exert its effects via serotonergic signaling. However, evidence exists that interaction with Sigma-1 may also represent a relevant mechanism of action. Thus, we aimed to determine the relative contribution of the interaction of fenfluramine with Sigma-1 by combination with the Sigma-1 antagonist 4-methoxy-3-(2-phenylethoxy)-N,N-dipropylbenzeneethanamine (NE-100).
Method: NMRI female mice (n=12-16) were fully kindled by stimulation via depth-electrode in the amygdala. Effects of E1R and fenfluramine were evaluated at different doses alone and in combination with NE-100. We administered all substances intraperitoneally with pretreatment times of E1R – 60' and NE-100 - 80'. Fenfluramine was evaluated at different pretreatment times. Tolerability tests focused on Rotarod test and selected Irwin score parameters.
Results: E1R increased generalized seizure thresholds (GST) in a dose-dependent manner (ED_{50}=35.25 mg/kg). All doses up to a maximum of 100 mg/kg were well tolerated. Effects of E1R on GST were partially abolished by NE-100. While we couldn't demonstrate a clear dose-dependency, fenfluramine increased afterdischarge thresholds (ADT) at 0.1 and 1 mg/kg, and GST at 10 mg/kg at the time of maximum effect (120´). In combination with NE-100, effects on ADT and GST were prevented. Adverse effects of fenfluramine were only observed at a higher dose (30 mg/kg).
Conclusion: Our findings indicate that positive modulation of Sigma-1 by E1R can exert acute antiseizure effects with an impact on seizure generation,
spread and termination. Furthermore, our results confirm that the interaction of fenfluramine with Sigma-1 can be relevant for its antiseizure activity.
Acknowledgements: Funded by DFG PO 681/12-1. E1R and fenfluramine were provided by LIOS and UCB/Zogenix, respectively.

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High frequency oscillations with frequencies 2000-8000Hz, physiology, biomarker

or artifact?

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Purpose: In the last decades high frequency oscillations (HFOs) in the ripple (80-250 Hz) and fast ripple (250-500 Hz) band were intensively studied as biomarkers of the epileptogenic zone. As the research continued it was found that there are also physiological HFOs and their occurrence is modulated by state of vigilance and cognitive tasks. With increasing sampling frequencies, we can explore HFOs in higher frequencies. In (Brazdil, 2017) Very fast ripples (500-1000 Hz) and ultra fast ripples (1000-2000 Hz) were found to be more specific biomarkers of the epileptogenic zone than HFOs in ripple and fast ripple band. Here we present oscillations with frequencies 2000-8000 Hz recorded from both epileptic and non-epileptic hippocampus with so far unknown clinical interpretation.
Method: We analyzed recordings from 8 patients from two centers implanted with microelectrodes (161 microcontacts on 12 electrodes) sampled at 25kHz. With our custom made detector of Ultra-fast oscillations (UFOs) we detected oscillations with frequencies ranging between 2000-8000 Hz from segments that did not contain movement artifacts. The detector was made to detect only oscillations creating isolated isles in normalized spectrograms. We compared the number of oscillations in epileptic hippocampi to non-epileptic hippocampi with the Mann Whitney U-test and Cliff's Delta effect size.
Results: We detected two types of oscillations. 835 oscillations which were not accompanied by lower frequencies and 2884 oscillations with sudden amplitude change and rapid damping. Out of 8 patients we had 2 patients implanted in epileptic hippocampi and 3 in non-epileptic hippocampi. There was no statistical difference between these two groups ($p>0.13$, effect size small) in any type of oscillations.
Conclusion: We detected so far unseen oscillations in the human hippocampus. There are still too few patients with such highly sampled recordings for clinical interpretation or proving their connection with hippocampal epilepsy.

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Compromised oligodendrocytes and myelination status in grey matter of type IIb focal cortical dysplasia: possible role in epileptogenesis

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Purpose: Loss of myelin and altered oligodendrocytes, the cells responsible for the myelin production, were reported in human tissues derived from different focal epilepsies. However, the myelination status was prevalently investigated in the white matter. Due to the important role of oligodendrocytes and proper myelin-coated axons in the extracellular potassium homeostasis, and the capability of high potassium accumulation to promote depolarization and seizures, it was hypothesized that demyelinated/less myelinated axons may contributed to set a condition of hyperexcitability. Thus, we characterized the grey matter myelination status in type IIb focal cortical dysplasia (FCDIIb), a developmental malformation and frequent cause of drug-resistant focal epilepsy, characterized by a well-known white matter pathology.
Method: We studied post-surgical FCDIIb neocortical specimens (n=12) comparing in all cases lesional and perilesion area in the same tissue section, using light and electron microscopy. Mature and precursor oligodendrocytes were evaluated by means of immunohistochemistry (PDGFRalfa, Olig2, MBP, CNPase antibodies) on paraffin sections. Ultrastructural investigation was performed in 6 cases to evaluate the number of myelinated axons and the presence of myelin sheaths abnormalities.
Results: Preliminary results show a reduction of the grey matter myelin fibers in lesion compared to perilesion. Moreover, a proportion of myelin sheaths exhibit interruption points and the myelin coating appear sometime thinner. Mature and precursor oligodendrocytes are also reduced in the core of lesion in comparison with perilesional areas.
Conclusion: These results indicate that: 1) in FCDIIb the myelination status is altered not only in the white matter, as previously demonstrated, but also in the grey matter. 2) These alterations, only present in the core of the lesion, seem to be part of the malformative spectrum observed in this dysplasia. We can speculate that the presence of less-myelinated axons may amplified and sustained tissue hyperexcitability. Electrophysiological data will be necessary to validate this hypothesis.

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Perineuronal nets abnormalities in epileptic human tissue

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Purpose: The extracellular matrix (ECM) plays several functions both during development and in the mature nervous tissue. In adult nervous system, ECM may be both dispersed in the neuropil and concentrated in lattice-like envelopes, called **perineuronal nets** (PNN) which surround the cell bodies and proximal dendrites of distinct subsets of neurons, mainly parvalbumin (PV)-positive GABAergic interneurons. **PNN** are proposed to serve multiple functions including regulating synaptic plasticity, stabilizing synapses and protecting neurons forming a physical barrier from potentially damaging neurochemical stimuli. During epileptogenesis, the

brain undergoes several changes including synaptic reorganization, which require structural plasticity, and PNN may play a role. Thus, we investigated PNN modifications in different human epileptic conditions.
Method: We analysed **aggrecan** expression, specific for adult PNN, in surgical specimens from 14 patients who underwent epilepsy surgery for drug-resistant epilepsy with different etiologies. In 9 patients the neuropathological diagnosis was **type II Focal Cortical Dysplasia** (FCDII), characterized by cito-architectural alterations and synaptic reorganization, and **cryptogenic** epilepsy in 5 cases, with no obvious MRI or histological alterations. For comparison, 4 **autoptic** brain samples from different area were considered. Immunohistochemistry, confocal microscopy and RNAscope technique was applied.
Results: In control autopsies a dense arrangement of aggrecan immunoreactivity (ir) was mainly present around PV interneurons with a clear decreasing gradient of expression from occipital to frontal and temporal areas. In FCDII, a significant increased ir was evident in the core of the dysplastic lesion in comparison to the adjacent perilesional area, crypto and controls. PNN were identified on PV interneurons but also around giant dysmorphic neurons presenting abnormal vGLUT1 and vGAT perisomatic basket formations. Conversely, in cryptogenic cases a reduction of PNN was observed.
Conclusion: These data support the notion that PNN remodeling and disruption are part of the epileptogenic changes and that their contributions to seizures is different according to etiology.

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Selective medial septum lesions in normal rats induce longitudinal changes in microstructure of limbic regions, behavioral alterations, and increased susceptibility to status epilepticus

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Purpose: The septo-hippocampal pathway is crucial for physiological hippocampal rhythms and is involved in epilepsy. Its clinical monitoring during epileptogenesis is complicated in humans. We aim to evaluate tissue changes after lesioning the medial septum (MS) of normal rats and how the depletion of specific neuronal populations alter the animals' behavior and their susceptibility to establish pilocarpine-induced status epilepticus.
Method: MS injection of vehicle or saporins (GAT1 or 192-IgG for GABAergic or cholinergic depletion, respectively, n=8 per group) in young adult SD rats. Diffusion tensor imaging (DTI) was obtained before surgery, and 14 and 42 days post-injection. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were evaluated in fimbria, dorsal (DH), and ventral hippocampus (VH). Between scan2 and 3, animals were submitted to the elevated plus-maze, open-field, rotarod, and water-maze. Toluidine and Timm staining used to analyze tissue alterations. Twenty-four different animals received pilocarpine to evaluate latency and severity

of status epilepticus two days after scan2.
Results: Increased DTI parameters in all regions during scan2 of all groups. Longitudinal changes during scan3 in FA maps of GAT1 and 192-IgG, showing significant reductions in DH (41%,p<0.05; 42%,p<0.05) and VH (36%,p<0.05; 38%,p<0.05) when compared to scan2. ADC values decreased in all groups; significant only in GAT1 (DH 17%,p<0.01; VH 22%,p<0.01; fimbria 22%,p<0.001). Behavior: 192-IgG spent more time in the center of the open-field box (p<0.001) and the open arms of the elevated-maze (p<0.05) when compared to all groups. GAT1 required more time to reach the water-maze platform (p<0.05). Histology: fimbria tissue damage and DH mossy fiber sprouting in GAT1. Epilepsy model: GAT1 reached status epilepticus faster and showed an increased mortality rate (70%).
Conclusion: Selective septo-hippocampal modulation impacts the integrity of limbic regions crucial for certain behavioral skills and could represent a precursor for epilepsy development.

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Caloric restriction as an alternative in the anjuvant therapy of the epilepsy due to downregulation of the *Wnt*/β-catenin pathway: evidence in hippocampus and cortex of kindled rats

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Purpose: Epilepsy is a common neurological disease, and despite all the therapeutic alternatives among medications, there are still 30% of patients with refractory epilepsy. Hence, alternative therapies such as caloric restriction (CR), whose antiepileptic mechanisms are not yet fully understood, must be sought. For instance, it has been shown that the Wnt/β-catenin pathway is hyperactivated in epilepsy. Therefore, the aim of our study is to determine whether caloric restriction plays a relevant role as a regulator of the canonical *Wnt* pathway.
Method: Male Wistar rats (n=24) were divided into 4 groups: control, Sham treatment (20% CR), Kindling *ad libitum* and Kindling 20% CR. The rats were sacrificed, the hippocampus and frontal cortex were harvested for quantification of proteins (*Wnt*, β-catenin, GSK3β, and cyclin D) by immunofluorescence and Western blotting methods. Protein quantification was performed using ImageJ software, and Excel was used for post-hoc ANOVA and Tukey statistical tests.
Results: From the electroencephalographic and behavioral point of view, we observed a shorter duration of seizures and an increased behavioral threshold (p<0.05) in the group kindling with caloric restriction. In protein analysis, the results showed a significant increase (p<0.01) in *Wnt* pathway proteins in the *ad libitum* kindling group compared with the rest, and a decrease in these proteins (p<0.01) to levels close to those of controls in the caloric

restriction kindling group.
Conclusion: CR can act as a regulator of the *Wnt* signaling pathway, inhibiting its activity in the hippocampus and cerebral cortex of kindled rats, thereby exerting an antiepileptic effect.

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The participation of Na^+ channels in epilepsy: a bibliometric analysis of the scientific production

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Purpose: Bibliometric analysis allows us to quantify and evaluate scientific activity in specific fields, so we know where to focus our efforts. Epilepsies are mostly idiopatic, genetic, as in Dravet syndrome, linked to sodium channels. With this in mind, this paper delves into the published articles related to the involvement of sodium (Na+) channels in epilepsy, in order to have a better perspective of this specific area.
Method: We followed up on the scientific production of epilepsy and the study of Na^+ channels in the SCOPUS databases. We extracted information regarding original articles from 2000 to 2022, using *epilepsy*, *seizure*, *epileptic*, *Na*, *sodium*, *channel*, *channelopathy* and *channelopathie*, as key words. From the articles obtained we depurated and categorized them (*mechanisms, drugs, genetics, case reports, tumors, diagnosis*, and *models*) to analyze the data.
Results: 290 original works were produced from 2000 to 2022. The greater contribution comes from the Unites States that specializes in *mechanisms*, followed by the United Kingdom with larger interest on *antiepileptic drugs*, just as the Netherlands. Overall, the most researched areas are *mechanisms* and *antiepileptic drugs*. Additionally, *type 1 sodium channel* is the most studied channel, and *new unnamed drugs* represent 50% of this production. On the other hand, we found that Nature Neuroscience is top cited journal having only one article, while Epilepsia Journal has 23 articles and 170 cites. Finally, the authors number per article ranges from one to sixty-four and 90% of publications belong to the experimental type.
Conclusion: Epilepsy is a disease that has been reported to affect developing countries in a significant way. The poorest countries have the highest rates of suffering from this neurological condition, which contrasts greatly with their scientific output in this area. This is likely due to technology or the condition's absence from the SCOPUS databases.

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Expression of antioxidant activity in the hippocampus of kindling rats with administration of S-allyl-cysteine and subjected to caloric restriction

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Purpose: Epileptic seizures are caused by excessive or simultaneous abnormal neuronal activity of a certain group of neurons. Oxidative stress plays a very important role in the pathophysiology of epileptic seizures due to a neuronal hyperexcitability increase, which could decrease by caloric restriction (CR). S-allyl-cysteine (SAC) administration has neuroprotective properties, after activating the Nrf2 factor and improving antioxidant activity.
Therefore, we analyzed the potential effect of SAC administration and CR in rats to reduce oxidative stress derived from epileptic seizures, induced by the Kindling model.
Method: 42 male Wistar rats were selected and organized into 7 groups; Control, Sham / CR, Sham / SAC, Kindling, Kindling / CR, Kindling / SAC, and Kindling/CR/SAC. The selected CR groups were given a 20% caloric restriction diet, while the SAC groups were administered a dose of 100 mg/kg/day intraperitoneally. Lastly, the Kindling groups were subjected to experimental epilepsy by the Kindling model. After dissection and tissue homogenization, protein quantification was performed using the Lowry method. Finally, the enzymatic (catalase, glutathione peroxidase and glutathione reductase) activity was measured by spectrophotometry.
Results: The antioxidant effect induced by the enzymatic activity was higher in the K/SAC group compared to the control group and Kindling in the sensorimotor cortex of rats, with a synergy in the dual action of both K/SAC/CR therapies.
Conclusion: SAC and CR are emerging therapies in the treatment of epilepsy that may favor both the reduction of seizures as well as the neuronal damage induced by the disease.
It is necessary to broaden research into non-pharmacological antiepileptic treatments in order to combat the high rates of refractoriness in such a frequent pathology.

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Pharmacochaperones restored GABA uptake from extracellular space and brain GABA homeostasis in epilepsy mice *SLc6a1*$^{+/S295L}$ and *Slc6a1*$^{+/A288V}$

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Purpose: Mutations in *SLC6A1* are associated with various epilepsy syndromes. We have extensively studied the molecular defect of the SLC6A1 mutations in cell and mouse models. We identified that a partial or a complete loss of the GABA uptake due to mutant protein destabilization and impaired trafficking is the major mechanism in cells. Characterization of the GABA reuptake in the live synaptosomes and gliosomes in the mutation knockin mice will provide critical insights into GABA homeostasis for the SLC6A1 mutation mediated disorders.
Method: HEK293T cells were transfected with recombinant GABA transporter-1 (GAT-1) cDNAs. The live cells are fluxed and evaluated for GABA uptake with ^{3}H radiolabeling GABA uptake assay. Total cell lysates were subjected to SDS-PAGE and immunoblotted for GAT-1 and

GFP. In the Slc6a1 mutation knockin mice, we isolated the live synaptosomes and gliosomes from the forebrain and measured the GABA uptake. We determined the level of GABA uptake in the mice treated with pharmacochaperones such as 4 phenylbutyrate (PBA) and TUDCA (taurousodeoxycholic acid).
Results: In cell models, the mutant GAT-1(A288V) had ~30% of remaining GABA uptake of the wildtype while the GAT1(S295L) had less than 3% of remaining GABA uptake compared with the wildtype. Both the GAT-1(A288V) and the GAT-1(S295L) proteins were retained inside endoplasmic reticulum with no or reduced cell surface expression. In mouse models, GABA uptake was reduced in the synaptosomes or gliosomes in both *Slc6a1*$^{+/A288V}$ and *Slc6a1*$^{+/S295L}$ mice. Pharmacochaperone treatment normalized the GABA uptake in both synaptosomes and gliosomes. Ongoing work is to determine the effect of TUDCA.
Conclusion: Both SLC6A1(A288V) and SLC6A1(S295L) caused reduced GABA uptake in cells due to ER retention of the mutant protein. In mice, both mutations caused reduced GABA uptake in synaptosomes and gliosomes, Slc6a1$^{+/A288V}$ and Slc6a1$^{+/S295L}$ mice had reduced GABA uptake but PBA treatment restored GABA uptake in both mice.

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Casein Kinase2 in mesial temporal lobe epilepsy: examining its contribution to hyperexcitability

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Purpose: Mesial temporal lobe epilepsy (MTLE) is the most common form of intractable epilepsy and is commonly conceptualized as the result of an imbalance between excitation and inhibition in the brain. NMDARs are key mediators of excitatory synaptic transmission in the brain. Studies suggest that CK2 inhibition reduced NMDAR activity. This study is designed to test the hypothesis that altered CK2 functions may contribute to hyperexcitability in MTLE.
Method: For this study, surgically resected tissue specimens of 23 patients and 17 controls (hippocampus tissues obtained from the post-mortem cases without any history of seizures or other neurological disorders) were obtained. mRNA levels CK2α, CK2β, NR2A and NR2B were evaluated by quantitative real-time PCR. Expression of proteins were studied by western blotting. CK2 activity was measured by kinase assay. Differential regulation of CK2 was also validated in Hippocampus, ATL and Neo cortex region of acute and chronic model of TLE.
Results: A significant increase in mRNA level of CK2α1 (3.48±0.63 fold, p=0.024), CK2β1

(2.50±0.43 fold, p= 0.03), NR2A (3.27±0.70 fold, p=0.01) and GLUR1 (2.48±0.47 fold, p=0.01) expression was observed in MTLE patients as compared to control. CK2α1, CK2β1, NR2A, NR2B phosphorylated and GLUR1 protein expressions were found to be increased in MTLE patients as compared to control ($p<0.05$). Kinase activity was significantly higher in MTLE patients ($p=0.003$). Same results were obtained for acute and chronic model of TLE.
Conclusion: Our results suggest that CK2 may contribute to hyperexcitability via modulating the regulation of NMDA receptors in MTLE. This new information greatly improves our understanding of the molecular mechanisms and synaptic plasticity involved in the pathogenesis of MTLE, and CK2 may represent new potential therapeutic targets for therapeutic strategies.

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Variations in the expression of Bcl-2 and caspase-3 in rats submitted to kindling epileptic model and treated with transcranial magnetic stimulation demonstrates a neuroprotective effect

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Purpose: Epilepsy is a neurological condition widespread throughout the world with at least 30% of those affected having a refractory response to drug treatments. Due to the above, there is interest in researching alternative therapies such as transcranial magnetic stimulation (TMS) which has shown a neuroprotective effect by mechanisms not yet well elucidated. Therefore, some Wistar rats were submitted to the epileptic Kindling model and treated with TMS with the objective of determining CASPASE-3 and BCL-2 variations in different brain regions such as cortex, hippocampus, and cerebellum as markers of cell death.
Method: 25 male Wistar rats were divided into 5 groups: Control, Kindling, SHAM-Kindling, Kindling + TMS and SHAM + TMS. After the animals were sacrificed, the cortex, hippocampus, and cerebellum were harvested for protein (BCL-2 and CASPASE-3) quantification by immunofluorescence and Western Blot analysis. The statical analysis was done by ANOVA.
Results: Rats submitted to kindling model show an increase of CASPASE-3 expression compared to the control group. On the other hand, when subjects were submitted to TMS the levels of CASPASE-3 show an important decrease while BCL-2 shows an increase, hence producing a neuroprotective effect, preventing or decreasing the number of cells that enter apoptosis.
Conclusion: Immunofluorescence and Western Blot analysis showed that BCL-2 levels significantly increased in the different brain regions of TMS treated rats, while CASPASE-3 expression results increased with Kindling model, and significantly decreased after being treated with TMS. Together, these mechanisms may help to regulate apoptosis, secondary to the epileptogenic mechanism.

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Autoimmune epilepsy - in vivo evidence from animal models that patient's IgGs induce general tonic clonic seizures, bind and kill neural cells

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Purpose: The aim of this study is to test if purified Immunoglobulins (IgG) of few young patients that suffer for many years from recurrent and intractable epilepsy, as well as severe neuropsychiatric impairments, and which often hospitalized due to all these, induce of their own General Clonic Tonic Seizures (GTCS) in normal rats.
Method: To test this, Normal rats underwent double surgery and implantation: first of EEG recording electrodes, and second – with osmotic minipumps pre-loaded with purified IgG of few epilepsy patients or of healthy controls. Then, the patient's IgG was released continuously (24/7) from the minipumps and reached the brain, during 1 week. EEG was recorded and analysed for seizure activity. At the end of the experiment, brains were removed and analysed histologically for: Binding and Brain damage caused by the patient's IgG.
Results: Our findings revealed that Patient's purified IgG induced on its own GCTS in 100% of the rats. The average seizure duration of 68 secs. The GTCS were most prominent in the 1st week, and declined gradually in the coming 3 weeks, in which the IgG was not released. The patient's IgG bound in vivo neural cells in several brain regions, and also killed neuronal cells and activated inflammatory cells, including activated astrocytes. The IgG of the control healthy individuals did not induce GTCS in any of the tested rats, and its binding and killing of neural cells was significantly lower, if at all.
Conclusion: IgG of young epilepsy patients with intractable epilepsy, cognitive deficits and psychiatric impairments induce by itself seizures and brain damage in animal model in vivo. As such, the autoimmune antibodies can be the sole cause of these pathological effects in the patients themselves.

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CD8+ T lymphocyte-driven attack on hippocampal interneurons leads to the development of inflammation-associated temporal lobe epilepsy

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Purpose: GABAergic interneurons are essential for the development and function of the

brain. The loss of interneurons in the hippocampus is considered a cause of the onset of temporal lobe epilepsy (TLE) because it shifts the excitation-inhibition balance. However, the exact role of interneurons in the development of limbic encephalitis which is often associated with TLE remains undetermined. We investigated whether a targeted attack of CD8+ T cells on interneurons leads to an LE phenotype with seizures and hippocampal sclerosis despite the lower proportion of interneurons compared to excitatory neurons. This assumption is based on the key role that interneurons play in regulating the hippocampal network.
Method: We established a mouse model by using a viral-mediated antigen transfer to express the model antigen Ovalbumin in hippocampal CA1 interneurons of transgenic mice carrying Ovalbumin-specific T cells. EEG/video monitoring followed by immunohistochemistry was used to determine the semiological and neuropathological consequences. Complementary, we analyzed the hippocampal mRNA expression of key genes involved in neuroinflammation, hyperexcitability as well as interneuronal markers by quantitative real-time PCR. Moreover, we applied patch clamp recordings in acute slices to characterize time-dependent changes in electrophysiological properties of the hippocampal network.
Results: With our new approach, we observed great specificity of interneuron targeting in vitro and in vivo, with no difference between interneuronal subtypes. Moreover, interneuronal expression induced a selective hippocampal CD8+ T cell attack on interneurons followed by dense T cell infiltration. Severe seizure phenotype accompanied neuronal cell loss in the CA1 region starting the third day after transfer. In addition, particular electrophysiological features were detected in the adjacent pyramidal cells associated with increased expression of inflammatory chemokines.
Conclusion: Selective interference of interneurons by T cells is sufficient to activate specific, inflammatory, and hyperexcitatory mechanisms and induce the development of LE with a strong seizure phenotype accompanied by overexpression of proinflammatory cytokines.

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The impact of a pre-existing *Toxoplasma gondii* infection in a self-sustained electrical status epilepticus mouse model of mesial temporal lobe epilepsy

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Purpose: The neurotropic parasite *Toxoplasma gondii* incurably infects one-third globally and is characterized by parasitic cysts in neurons and low-grade inflammation. Neuroinflammation plays a pivotal role in epileptogenesis and *T. gondii* is a risk factor for epilepsy; however, how a *T. gondii* infection influences the epileptogenic process is unknown. Therefore, this study aimed to elucidate whether a pre-existing *T. gondii* infection may alter the neuroinflammato-

ry environment, facilitate epileptogenesis, and worsen behavioral comorbidities in a self-sustained electrical status epilepticus (SSSE) mouse model of mesial temporal lobe epilepsy.
Method: Six-week-old male and female C57BL/6 Jax mice were intraperitoneally administered either *T. gondii* tachyzoites or PBS. At 4-5 weeks post-injection (i.e., once a chronic *T. gondii* infection was established), mice underwent electrode implantation, with a bipolar stimulating electrode placed into the right ventral hippocampus. At 6 weeks post-injection, mice underwent a 90-minute electrical stimulation through the bipolar electrode to induce status epilepticus (SSSE) or assigned to a control group. Mice were monitored for another 150 minutes before SSSE was terminated with diazepam. Video-EEG recordings were taken continuously between 0-4 weeks and 12-16 weeks post-stimulation. Behavior was assessed at 8-12 weeks, and neuropathology was assessed within 1 week and at 16-weeks post-stimulation.
Results: Both *T. gondii* and SSSE decreased sociability in male mice, and SSSE females had decreased social novelty compared to controls. In males, *T. gondii* and SSSE negatively impacted spatial learning and memory compared to PBS and controls, respectively. In females, SSSE and *T. gondii* increased anxiety levels. Preliminary evidence also indicates that *T. gondii* mice had increased spontaneous seizures.
Conclusion: Chronic *T. gondii* infection and SSSE negatively impacted numerous behavioral outcomes; however, this did not appear to occur in a synergistic manner. Analysis of neuropathology and EEG is ongoing.

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Microglia-derived C1q promotes epileptogenesis by increasing hippocampal inhibitory synapses pruning

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Purpose: The complement protein C1q has been shown to regulate synaptic pruning and phagocytosis in the CNS. Knockout of microglia-derived C1q has been reported to promote seizures and inhibit excitatory synapses pruning in the developing brain. However, it remains unclear whether C1q is involved in synaptic pruning in the adult epileptic brain.
Method: Western blotting was used to detect the expression of C1q in the hippocampus of KA-induced adult epileptic mice, and immunofluorescence was used to observe co-localiza-

tion of C1q with synaptic markers and microglia. Microglial C1q expression was knocked down using adeno-associated virus (AAV), followed by KA injection into the right hippocampus 4 weeks after AAV injection. The epileptic seizures of the mice were video-monitored and the local field potentials of the right hippocampus were recorded. Immunofluorescence was used to evaluate the number of excitatory and inhibitory synapses in the hippocampus of KA-induced epileptic mice. Patch clamp was used to detect AP, mEPSC and mIPSC in the hippocampal brain slices.
Results: The expression of C1q was increased in the hippocampus of KA-induced adult epileptic mice, and C1q was mainly co-localized with microglia. Downregulation of C1q expression in hippocampal microglia inhibited epileptogenesis, reduced the number of epileptic seizures, and decreased the number of hippocampal epileptic discharges. Immunofluorescence staining revealed that downregulation of C1q expression in hippocampal microglia increased the number of inhibitory synapses (co-expression of VGAT and Gephyrin), but did not affect the number of excitatory synapses (co-expression of Vglut1 and Homer1). Furthermore, the co-localization of C1q and inhibitory synapses and the number of inhibitory synapses engulfed by microglia were reduced. Patch clamp of mouse brain slices also showed that downregulation of C1q expression increased mIPSCs, but had no effect on mEPSCs.
Conclusion: These results suggest that microglial C1q promotes epileptogenesis by increasing inhibitory synapses pruning in the hippocampus of KA-induced adult epileptic mice.

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An effect of Sulforaphane on neurovascular regulation and energy metabolism during seizures in rats

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Purpose: As around 30 % of epilepsy patients do not respond to the anti-seizure medication, there is a need for the development of new therapeutic venues. As many anti-epileptic drugs primarily focus on seizures, in our previous work we were trying to interfere with the processes known to occur in epileptogenesis, namely energy metabolism changes, using Nrf2 activation with sulforaphane (SFN). We discovered that sulforaphane can reverse epileptogenesis-induced metabolic changes as revealed by FDG PET in immature rats. In this work, we decided to treat both adult and immature rats with the SFN and perform an assessment of cerebral blood flow (CBF) responses using Laser Doppler Flowmetry (LDF) when the animals underwent transcallosal electrical stimulation as well as electrophysiological recording,
Method: In the case of LDF, two stimulating electrodes were placed above the MCx/SCx and LDF probe was placed on the contralateral side. Subsequently, we performed a series of incrementally increasing electrical stimulations and a series of 15s lasting stimulations at 8Hz in

fast succession to mimic status epilepticus. We further examined the impact of SFN pretreatment on the excitability eliciting evoked potentials (75-6000 mV), paired pulses (50-500 ms) and a number of spike-wave discharges after 15s/8Hz electrical stimulation.
Results: We found that SFN significantly increased the amplitude of CBF responses and CBF itself compared to the blank group. However, SFN had a very limited impact on the electrophysiological parameters when measured 1 h and 24 h after its application, rendering itself as not having a direct anti-seizure effect, as the slight non-significant improvement could be a result of increased neurovascular coupling.
Conclusion: Nevertheless, SFN warrants further attention as it shows potential as a powerful anti-epileptic drug, as shown by our work and others working with Nrf2 stimulators.
The work was supported by a grant from the Czech Science Foundation no. 22-28265S.

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Levetiracetam modulates adenosinergic pathway to ameliorates epileptogenesis: *in silico* and *in vivo* mechanistic study in model of epilepsy

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Purpose: The purpose of this study was to investigate the possible mechanisms in which levetiracetam affects the adenosine signaling systems in an animal model of epileptogenesis.
Method: The study was divided into three major phases, i.e., *in silico* studies, acute *in vivo* studies, and a kindling model of epileptogenesis. In the docking studies, the possible interactions of levetiracetam with A1R and ENT1 were predicted. In the acute seizure model, the reversal of the antiseizure effects was determined by the adenosine receptor antagonists. The molecular changes were determined at the end of the kindling model to determine the gene expression analysis and protein quantification of A1R, ENT1, and Kir3.2 using RT-qPCR and immunohistochemistry, respectively.
Results: The docking studies predicted a possible interaction of levetiracetam with the A1R and ENT1. Caffeine (100 mg/kg) and 8-cyclopentyl-1,3-dipropyl xanthine (DPCPX) (25 mg/kg) reversed the antiseizure effects of levetiracetam by lowering the% protection and delaying the onset of the first myoclonic jerk and generalized clonic seizures, according to the findings of the acute study. In PTZ-induced kindling, levetiracetam significantly increased the gene expression of A1R, Kir3.2 while decreasing the expression of ENT1 in the hippocampus and cortex. Protein expression in the hippocampus and cortex revealed increased expression of A1R and decreased expression of ENT1.
Conclusion: Based on these results, it can be concluded that levetiracetam modulates epileptogenesis by acting on the adenosine pathway in CNS.

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Anticonvulsant effect of cannabidiol after lateral fluid percussion brain injury in rats

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Purpose: **Purpose:** Traumatic brain injury (TBI) is a significant risk factor for acquired post-traumatic epilepsy (PTE). However, the mechanisms that lead to PTE are highly complex; no drug treatment has been able to prevent late seizures. Cannabidiol (CBD), a major non-psychoactive component of *Cannabis sativa*, has a broad spectrum of therapeutic potential, including neuroprotective effects. Therefore, we aim to investigate the therapeutic potential of CBD on pentylenetetrazol (PTZ)-induced seizures after TBI.

Method: **Methods**: Forty adult male Wistar rats were submitted to stereotaxic surgery, and a burr hole of 3 mm diameter was drilled on the right convexity (1.5mm AP; 1.2mm LL), and a cannula was fixed in the hole. After 24h, the head trauma was applied through the lateral fluid percussion device attached to the cannula. CBD (5mg/kg,i.p.) was given for five days, and started 24h after head trauma. Thirty days after the trauma, animals received PTZ (35mg/kg,i.p) as a second hit to induce convulsive seizures.
Results: Behavioral seizure analysis indicated a reduction in seizure incidence in the TBI-CBD group by 17% compared with the TBI-Sal group. CBD also reduced the number of animals presenting severe seizures, although there were no significant differences. One-month post-TBI, the number of parvalbumin (PV)-positive interneurons in the cortex of the TBI-Sal group was reduced compared with Sham-CBD ($p< 0.05$).

Conclusion: Five-day-treatment with CBD after the TBI reduced seizure incidence, even 30 days before PTZ induction. Moreover, TBI induced a loss of PV interneurons in the cortex, whereas CBD seems to increase the number of PV. Although promising, more studies are needed to suggest a CBD therapeutic potential for PTE after TBI.

Funding: FAPESP;VS (2022/10520-0); SR (2017/05242-3). This work was supported by FAPESP, CAPES, and CNPq.

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The effect of miR-324-5p antagonism in epileptogenesis

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Purpose: Epilepsy is often caused by an initial brain insult followed by epileptogenesis and finally the development of spontaneous recurrent seizures. The details underlying epileptogenesis remain largely unknown. MicroRNAs regulate mRNA translation and stability and are often altered in epilepsy. We have shown that antagonism of a specific miRNA, miR-324-5p, before brain insult and in a model of chronic epilepsy decreases seizure susceptibility and frequency. Here we tested the hypothesis that antagonism of miR-324-5p inhibits epileptogenesis following a brain insult.
Method: We used the intrahippocampal kainic acid model to induce epileptogenesis in wild type male mice aged 6-8 weeks. Twenty-four hours after *status epilepticus*, we administered a miR-324-5p or scrambled antagomir intracerebroventricularly and implanted cortical surface electrodes for EEG monitoring. EEG data from 12 mice per group was collected for 28 days and analyzed for seizure frequency and duration as well as interictal spike activity and EEG power. Mouse brain tissue was collected for assessment of neuronal cell death and gliosis. Parallel experiments used similar approaches combined with ribosomal tagging to identify the miR-324-5p-dependent molecular networks altered during epileptogenesis.
Results: Results indicate high levels of variability in seizure onset, frequency, and duration and no significant effect of antagomir treatment. Analyses of more subtle changes, e.g. in spikes, hippocampal morphology, and molecular signaling are ongoing.
Conclusion: Our results suggest that despite playing an important role in reducing seizure susceptibility and seizure frequency in chronic epilepsy, miR-324-5p inhibition may not be sufficient to stop epileptogenesis. Many miRNAs have been implicated in epilepsy and it is likely that antagonism of miR-324-5p alone is insufficient to result in complete inhibition of epileptogenesis. Future work is needed to assess whether combined inhibition of several epileptogenic microRNAs leads to more complete prevention of epileptogenesis.

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Inter-ictal epileptiform discharges are the most relevant marker of the epileptogenic zone in stereo-electroencephalography: a data-driven analysis

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Purpose: Recently, a multi-feature approach combining interictal epileptiform discharges (IEDs), high-frequency oscillations (HFOs) and connectivity features showed promising results in the localization of the epileptogenic zone (EZ). However, which of these features are the

most important is not well understood yet. Here we used an objective, data-driven approach to investigate the feature importance in machine learning models across different states of vigilance.
Method: We analyzed stereo-electroencephalography recordings from 18 consecutive patients with Engel1A post-surgical outcome. For each patient, 5-min long interictal segments of awake, non-rapid eye movement sleep (N2+N3), N2, N3, REM, maximum and minimum spiking rates. For EZ localization, we used a support-vector-machine model combining IEDs, HFOs, spectral power (SP) features and connectivity features. The EZ was defined as resected seizure-onset zone contacts. The performance was evaluated by the area under the precision recall curve (PRAUC). Features were grouped by a hierarchical clustering on the Spearman rank-order correlations. The best performing feature within each group was identified by outliers of the ANOVA F-score values.
Results: On average, the model achieved a score of 0.4863 PRAUC. The algorithm detected three main clusters of closely correlated features: (1) connectivity features, (2) SP features, (3) IEDs, HFOs, spectral entropy and phase-amplitude coupling features. These three clusters were consistent across all states of vigilance. The best performing feature across all states were IED rates. The other most frequently selected features were relative entropy (REN) in the gamma band and SP in the fast ripple band. REN of broadband signal was preferred in REM and minimum spiking rate segments, and REN in ripple band was selected in N2. Furthermore, SP in beta was preferred in N2 and minimum spiking rate segments.
Conclusion: Our results show three main clusters of features, which were stable across states of vigilance. Overall, IED rates were the most relevant feature for EZ localization.

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Functional connectivity and plasticity changes in focal epileptogenic zones

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Purpose: In recent years, research on ictogenesis fueled novel concepts of understanding epilepsy as a network disease. Epileptic seizures originate from altered network structures at the level of macroscopic and microscopic brain circuitries. Recently it has been shown that different neuronal subpopulations contribute differentially to the development of epileptogenic network. However, we still lack electrophysiological hallmarks from the microcircuitry to unambiguously delineate the epileptogenic brain region within this network. Currently, epileptiform potentials (EP) and high frequency oscillations (HFO) are used for defining the EZ during epilepsy surgery. However, both these biomarkers can be recorded beyond the ictal onset zone within the EZ. Therfore, further electrophyisiological biomarkers are needed to locally define the EZ and therewith help to delineate the minimal resection area during surgery.
Method: Here we develop computational models that allow assessing functional connectivity and plasticity in neural micro circuitries using spike-timing dependent plasticity (STDP) learning rules. Using a Bayesian framework, we infer the neural connections and changes in STDP

from human single neuron recordings inside and outside the epileptogenic zone.
Results: As a first step, we simulate neural spike data with the similar statistical properties as the data recorded in humans. In these data, we show that the model reliably captures connectivity and plasticity properties. Next, we infer connectivity properties and learning rules from human data. We show that these rules align with experimental results in rats and other animals. Furthermore, we observe a trend between increasing patient age and increasing maximum synaptic modification indicating that the model is able to map individual network properties.
Conclusion: Applying the model on data from epileptogenic regions will now allow us to asses connectivity and STDP parameters connected to the EZ and potentially to the process of ictogenesis.

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Analysis of the activity of individual hippocampal neurons during epileptic seizures in patients with drug-resistant epilepsy candidates for surgery

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Purpose: Patients with focal drug-resistant epilepsy could benefit from surgical treatment if the epileptogenic zone (EZ) is identified. Intracranial electroencephalography with macro-microelectrodes allows the recording of local field potentials (LFP), the extracellular activity of multiple neurons (MUA) and the activity of single neurons (SN).
The purpose of this research was to evaluate the behavior of SN during epileptic seizures.
Method: Macro-microelectrodes were implanted in patients with drug-resistant epilepsy and the signal was recorded with the Cervello system filtered between 1-9000 Hz and sampled at 30 kHz. SN activity were analyzed in 100-ms windows from 5 min before ictal onset and 1 min after in the ictal onset zone (IOZ) and in the propagation zone (PZ). Firing rates (FR), stereotypy, and Fano Factor (FF) were determined. The signal was processed in MATLAB using WAVE_CLUS and FieldTrip.
Results: A total of 150 SN from 4 patients in 59 seizures were analyzed, 78 in IOZ and 72 in PZ. As for the firing rate, three distinct ictal patterns of the SN were identified: increased, decreased and unchanged FR. The FF showed a significant increase in the neurons involved in the IOZ. All neurons involved in the IOZ showed a high degree of stereotypy.
Conclusion: The analysis of the behavior of the SN allowed to describe patterns of ictal activity, contributing to understand the dynamics neural networks during seizures. Future analyzes could identify biomarkers of the EZ at the microscale.

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The differences in noradrenaline levels in wistar and genetic absence epilepsy rats

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Purpose: Monoamines, the major neuromodulators in the central nervous system, are all known to play a role in epilepsy. Several studies have indicated that the noradrenergic system is affected in different types of epilepsy. We investigated the noradrenaline levels in different brain regions in Genetic Absence Epilepsy Rats from Strasbourg (GAERS) which is the well-validated genetic model of absence epilepsy and compared them with Wistar rats in order to detect whether is there any differences or not.
Method: Adult male non-epileptic Wistar rats (n=6) and GAERS (n=6) weighing between 250-350 g were used in the experiments. After transcardiac perfusion, the brains were removed and the cortex, thalamus, and hippocampus regions were immediately dissected for analysis of noradrenaline levels by using the high-performance liquid chromatography **(**HPLC) method.
Results: HPLC results showed that the noradrenaline level in the hippocampus of the Wistar group was detected to be significantly higher than in the GAERS group. Noradrenaline levels in the cortex and thalamus were not significantly different in GAERS rats than in Wistar rats.
Conclusion: Our study showed that noradrenaline levels in the hippocampus in the Wistar group are higher than in GAERS rats. Further research in different brain regions can be enlightening to understand better the role of noradrenaline in epilepsy.

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Intracerebroventricular administration of anti-leucine-rich glioma inactivated-1 protein antibody increases seizure susceptibility and impairs memory in rats

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Purpose: Anti-leucine-rich glioma inactivated 1 (anti-LGI1) encephalitis is a neuroimmunological syndrome associated with memory impairment and pharmacoresistant seizures. In this study, we aimed to clarify the role of LGI1 antibodies on epileptogenesis and cognitive performance in the passive transfer rat model.
Method: IgG purified from the peripheral blood of anti-LGI encephalitis patients and healthy

controls (HC) were intracerebroventricularly infused into non-epileptic Wistar rats for 10 days along with the EEG recordings. Behavioral assessments were performed before and after IgG administration. After the IgG administration seizure susceptibility was evaluated with a single convulsive dose (45 mg/kg) of pentylenetetrazol (PTZ). Acutely induced epileptic discharges and seizure stages were evaluated and compared between groups.
Results: No spontaneous activity was observed in cortical EEG during and after the antibody infusions. PTZ-induced seizure stage was significantly higher in the LGI-1 antibody groups compared to the HC group ($p<0.001$). In addition, vertical activity in open field maze, spontaneous alternation in Y-maze, and discrimination index in novel object recognition test were significantly different in LGI1 antibody group ($p<0.05$).
Conclusion: These findings provide evidence that neuronal surface LGI1 antibodies appear to increase the susceptibility of seizures as well as disrupt memory and motor functions. Here developed LGI1 antibody-mediated passive transfer autoimmune encephalitis rat model can be considered as a potential in-vivo model for anti-LGI1 encephalitis.

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Impaired response to mismatch novelty in the Li^{2+}-pilocarpine rat model of TLE: correlation with synaptic remodelling and hippocampal monoamines

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Purpose: Novelty is an important stimulus in episodic memory formation. Mismatch novelty detection activates the hippocampal CA1 area in humans, influences rodent hippocampal synaptic plasticity *in vivo* and is vital for memory reformulation and reconsolidation. Mismatch novelty detection is impaired in patients with hippocampal lesions. In this work we investigated the response to spatial mismatch novelty, as occurs with the new location of known objects in a familiar environment, in the Li^{2+}-pilocarpine rat model of TLE and its correlation with hippocampal monoaminergic markers.
Method: Behavioural testing of spatial learning and mismatch novelty responses was performed in rats showing Li^{2+}-pilocarpine induced spontaneous recurrent seizures (SRSs) for at least 4 weeks (Serpa et al., 2022, Neurochem. Int., 158:105383). Mismatch novelty responses were evaluated in a holeboard by evaluating exploratory activity upon detection of familiar objects presented in a new location. Hippocampal monoaminergic nerve terminals were identified by western blot in hippocampal synaptosomes obtained from Sham and SRS rats.
Results: SRS rats displayed impaired spatial learning in the radial arm maze (RAM) and impaired mismatch novelty responses (absence of enhanced nose pokes in holeboard exploration). Conversely, novel object recognition was not affected in SRSs rats, for which no differences in object preference were observed relative to Sham controls. The levels of synaptic tyrosine hydroxylase were enhanced to 199.8±24.4% ($P<0.05$), while the serotonin and dopamine transporters were decreased to 70.5±4.2% ($P<0.001$) and 82.3±4.5% ($P<0.05$), in

the hippocampus of SRS rats as compared to Sham controls.
Conclusion: This study demonstrates that mismatch novelty detection is particularly affected by seizure recurrence and that this correlates with decreased serotonergic and dopaminergic (and anticipated enhancement of noradrenergic) hippocampal content. This suggests that deficits in spatial mismatch novelty detection may substantially contribute to cognitive impairment in MTLE and that altered monoaminergic transmission may be involved in these changes.

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Effects of anatolian propolis on absence seizures and anxiety in rats with genetic absence epilepsy

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Purpose: The propolis originating from Anatolia has a very high degree of phenolic constituents including caffeic acid phenethyl ester (CAPE) that exhibits neuroprotective potential through its anti-inflammatory and antioxidant activities. In this study, the effect of Anatolian propolis on absence seizures and anxiety levels were investigated in Genetic absence epilepsy rats from Strasbourg (GAERS).
Method: Raw and commercial Anatolian propolis samples were used. 30% (180mg/kg/day) and 15% (120mg/kg/day) samples of Anatolian propolis and the same volume of tap water for the control group were administered by oral gavage to adult GAERS for 35 days. The effect of Anatolian propolis on seizure duration, number and mean seizure duration was evaluated on the EEG and compared with the control group. Anxiety levels were assessed with the elevated plus maze test. At the end of the recording session brains were isolated and freshly frozen in order to measure the interleukin-1-beta (IL-1β) levels by ELISA.
Results: Oral administration of propolis at two doses decreased the seizure duration and number in adult GAERS after 35 days of subchronic administration ($p<0.05$). Anxiety levels did not showed difference compared to control group.
Conclusion: This is the first study evaluating the effects of Anatolian Propolis on absence seizures in GAERS. Our results suggest that Anatolian propolis may have therapeutic benefits in alleviating absence seizures in GAERS. Further research is needed in order to understand the mechanisms underlying this potential benefit.
This project was supported by TUBITAK-2209A University Students Research Projects Support Program.

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Ex vivo electrophysiological studies in resected perioperative human brain tissue samples

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Purpose: Considerable circuitry differences exist between human and rodent brain tissue, which may hinder translation of scientific discoveries to clinical practice. *Ex vivo* human brain tissue allows experimental investigation of pathophysiological mechanisms. In particular, an assessment of the contribution of synaptic transmission at the level of the microcircuit and its relationship to seizure activity is achievable.
Method: Patients undergoing epilepsy (n=12) or tumour (n=2) surgery provided written informed consent for sample donation. Perioperative neocortical tissue specimens were transported to the laboratory in carbogenated artificial cerebrospinal fluid (ACSF), where brain slices (400 µm) were prepared and maintained. Extracellular local field potentials were recorded from macroscopically visible grey matter before seizure like events (ictal discharges; ID) were evoked with modified ACSF (mACSF; 0.2 mM Mg^{2+}/8 mM K^{+}). Seizure features; event duration (mins), inter-event duration (mins), highest spike amplitude (mV), and area under the curve (μV^2/Hz) were analysed. Data are given as mean ± SEM.
Results: No spontaneous IDs occurred *ex vivo*. Evoked ID recordings were obtained in tissues from 8 out of 14 study participants. The average time for IDs to emerge after switching to mACSF was 28.8 ± 3.26 min. Baseline ID characteristics across slices show a mean duration of 2.21 ± 0.12 mins, and an average duration of 3.30 ± 0.76 mins between IDs. Mean highest ID spike amplitude was 2.67 ± 0.47 mV, and Fast Fourier transformations demonstrated an average ID power value of 0.60 ± 0.42 μV^2/Hz. Pharmacological inhibition of the AMPA/kainate receptor (NBQX, 1 µM) suppressed ID activity (n=2).
Conclusion: Using an established model, we have successfully recapitulated seizure like events from perioperative human brain tissue for the first time in Ireland. Future work will aim to optimise this approach and explore novel pharmacological anti-seizure therapies using this translational technique.

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The molecular mechanisms involved in Dravet syndrome rhythmicity

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Purpose: More than 70% of children with Dravet Syndrome (DS) experience sleep disturbances. Sleep-wake cycles commonly span over 24 hours, which may be linked to the circadian cycles. Levels of the core clock genes, which regulate the circadian cycles, are decreased in acquired epilepsy, and evidence suggests that it may impact epileptogenesis. The molecular profile of the core clock machinery and whether its disruption could trigger seizures and other phenotypes remains unknown in DS. Here, we have profiled the expression of key core clock genes in a DS mouse model at an age relevant for the development of epilepsy.
Method: F1. Scn1a(+/-)tm1Kea mice were generated by crossing Scn1a(+/-)tm1Kea male (129S6/SvEvTac) with inbred C57BL/6JOlaHsd female. To assess the molecular clock profile, wildtype (WT) and Scn1a(+/-)tm1Kea (n=4/group) were transcardially perfused at the same time-of-day on the postnatal day 21 (P21). The right and left cortices and hippocampi were micro dissected for the analysis of the core clock machinery (i.e., Bmal1, Clock, Per1, Per2, Cry1, Cry2) by qPCR and western blotting, respectively. Data was analysed by Student t-test, as appropriate. $P<0.05$ was considered as significant.
Results: The positive clock regulators Bmal1 and Clock were significantly decreased in the hippocampus, but not cortex, of P21 Scn1a(+/-)tm1Kea mice in comparison to WT ($P<0.05$). No statistical difference was found in the expression of all the other clock genes investigated (Per1, Per2, Cry1 and Cry2; $P>0.05$) at this age and time-of-day.
Conclusion: Bmal1 is essential for maintaining the mammalian molecular clock. Here, we showed molecular clock dysregulation in the DS mice hippocampus at an age relevant for epileptogenesis and increased risk of sudden unexpected death in epilepsy. To fully understand how these region-specific disruptions might lead to the relevant phenotypes, future studies are needed.

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Hippocampal T2 relaxation correlates with the levels of functional astroglial proteins in patients with mesial temporal lobe epilepsy

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Purpose: Mesial temporal lobe epilepsy is the most frequent focal pharmacoresistant epilepsy with surgical indication. Most patients have hippocampal sclerosis, characterized by reduced volume and increased T2 signal on preoperative MRI. Since gliosis is often associated with the increased T2 signal, we aimed to compare whether functional glial markers such as metallothioneins I and II (MT-I/II) and the glutamate transporter EAAT2 had a stronger correlation with the T2 signal than the expression of the structural astroglial protein GFAP.
Method: Patients with temporal lobe epilepsy and hippocampal sclerosis (n=44) who underwent axial multiecho T2 MRI scan at a 3 Tesla machine (TEs = 20-100 ms; TR = 3000 ms; voxel = 1x1x3 mm) were selected. Hippocampal sections were submitted to immunohistochemistry

for the detection of EAAT2, MT-I/II, and GFAP proteins. T2 relaxation time, and immunostaining intensity for selected glial proteins were quantified.
Results: Twenty patients had T2 relaxation within normal range (107.4±6.9 ms) and 22 had increased hippocampal T2 relaxation (132.6±13.4 ms). Cases with increased T2 relaxation had higher GFAP staining in CA2 (p=0.03) and a trend towards reduced EAAT2 staining in CA4 and increased MT-I/II expression in CA2 (p>0.05). Hippocampal T2 relaxation time correlates positively with the immunostaining for MT-I/II (r=0.507, p=0.005), and GFAP (r=0.371, p=0.043) in CA2 and negatively with EAAT2 in CA4 (r=-0.373, p=0.016). A stepwise linear regression indicated that the combination of MT-I/II immunostaining in all CA subfields, EAAT2 immunostaining in the granule cell layer, CA4-CA2, and the subiculum, and GFAP immunostaining in CA4 explain 77% of the hippocampal T2 relaxation (r=0.88, p<0.0001).
Conclusion: Our study indicated that the increased T2 relaxation is strongly related to functional rather than structural astroglial proteins.

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Hyperphosphorylated tau protein, autophagy inhibition and somatic mutations in mTOR pathway in focal cortical dysplasia type II (FCDII)

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Purpose: mTOR pathway overactivation and mutations in associated genes are known features of FCD. Hyperphosphorylated tau is present in focal epilepsies and is associated with cognitive decline. Interestingly, mTOR overactivation and tau phosphorylation relate to cognitive decline in Alzheimer's disease. We hypothesise that overactivation of the mTOR pathway may be one of the mechanisms for increased phosphorylation of tau in FCD. We present mTOR mutations, expression of phospho-tau, and correlate this with clinical data in a cohort of FCD patients.
Method: We conducted immunohistochemistry with AT8, p62 and Beta Amyloid on surgical tissue from 54 FCDII cases. Moreover, DNA extraction and targeted, next-generation sequencing with a panel against mutations in mTOR pathway genes were performed on tissue from 48 FCDII cases. Eight cases were selected for double immunofluorescence labelling using markers for phospho-tau and mTOR activation (pS6).
Results: Total tau load (AT8) was found to significantly correlate with patient's age at surgery (r = 0.449, p<0.0009). Immunohistochemistry with p62 marker of autophagy inhibition showed a varying pattern of cytoplasmic and nuclear staining in balloon cells, and dysmorphic neurons with significantly higher number of balloon cells with positive nuclei than dysmorphic neurons (p<0.0001). Balloon cells showed higher prevalence in white matter than grey

matter. Double immunofluorescence staining indicated co-localisation of hyperphosphorylated tau and mTOR activity. Both somatic and germline mutations in mTOR were identified.
Conclusion: Phospho-tau load in FCD was correlated with age– a possible consequence of epilepsy duration. Reduced autophagic flux was more prominent in cell populations characteristic of FCDII possibly due to mTOR pathway overactivation.

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Myeloid differentiation factor 88 knockout decreases seizure's duration and intensity, thereby increasing survival during status epilepticus

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Purpose: To compare C57/BL6 mice to their immunodeficient counterpart myeloid differentiation factor 88 (MyD88) knockout, in the severity of status epilepticus caused by PTZ injection..
Method: Male c57/bl6 (N=11) and MyD88 knockout (KO) (N=10) mice weighing 15-30g were used (CEUA 8821070122). After receiving intraperitoneal injection with GABA-A receptor antagonist pentylenetetrazole (80mg/kg) the following prolonged seizure of 30 min duration was recorded and analyzed by three unaware observers, to measured the quantity of first seizure latency and duration, mortality, amount of stage 5 Racine scale seizures, death latency as well as if tonic-clonic seizures were reached.
Results: MyD88 KO showed notable delay in 1st seizure latency [($P < 0.05$) 0,0075 ** Difference between means (B - A) ± SEM 117,7 ± 112,0)] but not in 1st seizure duration [($P > 0.05$) 0,1776 Difference between means (B - A) ± SEM 5,564 ± 6,569]. MyD88 mortality was 50% compared to 72.73% in controls, possibly because of the higher quantity of type 5 seizures [($P < 0.05$) 0,0124 * Difference between means (B - A) ± SEM-1,318 ± 0,7098] in controls. Although for the deceased animals there was similar death latency in both groups [($P > 0.05$) 0,2829 Difference between means (B - A) ± SEM8,150 ± 301,0]. All animals reached at least one tonic-clonic seizure.
Conclusion: Pentylenetetrazole intraperitoneal administration induced status epilepticus, and it was observed that MyD88 inflammatory protein knockout caused an important impact for increasing survival, possibly caused by a delay in seizure latency and severity. Considering the roles of MyD88 in neuroinflammation, herein we were able to evidentiate a close relationship between status epilepticus and the immunological system.

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MicroRNA-142-5p and its effect in male & female rats on the progression of status epilepticus

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Purpose: MicroRNAs are short non-coding RNAs (18-22 nucleotides) playing a vital role in gene regulation. Besides microRNA expression, sex-dependent response in the disease progression needs to be characterised. Previous experiments on animal models undergoing status epilepticus (SE) showed that miR-142-5p is highly dysregulated, suggesting its crucial role during seizure progression. In order to assess the effect of miR-142-5p, the antagomir molecules were applied to inhibit its effect. This study describes the impact of miR-142-5p inhibition on the progression of the acute phase of SE in animals on postnatal day 12 (P12) with an additional description of differences between male and female rats.
Method: P11 animals (at least four in the group) were administered with either antagomir-142-5, scramble-antimiR, saline, and LiCl (125 mg/kg IP). P12 animals were implanted with cortical electrodes under ether anaesthesia and, after rest, connected to EEG with background registration followed by administration of pilocarpine (35 mg/kg IP). Paraldehyde administration (0.07 ml/kg IP) was after 90 minutes. The SE occurrence, its latency, peak values, and the occurrence of seizures and their characteristics were monitored.
Results: Results show that a higher dose (0.4 ng) of antagomiR-142-5p significantly affects the suppression of SE in males compared to female infantile rats. Only 2 out of 10 infantile male rats exhibited electrographic seizures and entered SE, while all female rats progressed to these symptoms. On the other hand, low-dose (0.2 ng) antagomiR-142-5p administration led to significantly shorter SE latencies in males ($p=0.03$).
Conclusion: Our results indicate that a higher dose of agomiR-142-5p had a modulating effect in immature male but not female rats. Our future investigation of this phenomenon will focus on determining the source of the sex difference in our model.
Acknowledgements: This work has received funding from Czech Science Foundation, project no. 23-05274S

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Investigating the harmaline-induced tremor in genetically epileptic WAG/Rij Rats

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Purpose: Harmaline-induced tremor is the most commonly used model of essential tremor.

Harmaline produces rhythmic firing in inferior olive neurons, activates the olivo-cerebellar glutamatergic climbing fibers, leads to the degeneration of the Purkinje cells, and results in disinhibition of the deep cerebellar nuclei. This disinhibition increases rhythmic activity of the thalamus which leads to the consequent tremor. WAG/Rij rats, a genetic model of absence epilepsy, display spontaneous spike-wave-discharges (SWDs) which attributed to the cortico-thalamocortical structures. The cerebellum may be involved in modulating the activity of brain regions linked to SWDs, such as the thalamus and the cerebral cortex. The aim of the study was to evaluate the harmaline-induced tremor in WAG/Rij rats and to examine the effect of harmaline on the occurrence of SWDs.
Method: To evaluate harmaline-induced tremor, WAG/Rij (n=5) and Wistar (n=6) rats received a single injection of harmaline (20 mg/kg,ip). The percent duration, intensity, and frequency of tremor were evaluated by a custom-built tremor and locomotion analysis system. To evaluate the effect of harmaline on the occurrence of SWDs, separated groups of WAG/Rij rats were injected either with harmaline (1 mg/kg, 16 mg/kg, or 32 mg/kg, n=5 each group) or saline. For EEG recording, epidural electrodes were stereotaxically implanted 1-week before the tremor induction.
Results: The duration and intensity of harmaline-induced tremor were significantly lower in WAG/Rij compared to Wistar rats ($P<0.0001$) whereas no difference was observed in tremor frequency between two strains ($P>0.999$). Moreover, 16 mg/kg and 32 mg/kg harmaline injections decreased the number and the cumulative duration of SWDs in WAG/Rij rats ($P<0.0001$).
Conclusion: Our study found that harmaline-induced tremor was significantly less intense in WAG/Rij rats compared to Wistar rats and harmaline decreased the number and duration of SWDs. These findings suggest a reciprocal interaction between the cerebellum and other brain regions related to the occurrence of SWDs.

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Early warning signals of critical transitions in iEEG of mice with focal cortical dysplasia type II

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Purpose: Unpredictability of seizures constitutes a major disabling factor for people with epilepsy. From the perspective of dynamics of complex systems, seizure onset is a critical transition. Thus, during the pre-ictal period, early warning signals of critical transition might be detectable in the form of so-called critical slowing which is marked by increasing variance, lag-1 autocorrelation, and spatial correlation of the signal. Existence of critical slowing is still a matter of debate. However, long-term analysis of its markers was successfully used for forecasting of seizure risk. We analyzed these markers in iEEG recorded in a mouse model of focal

cortical dysplasia type II (FCD).
Method: FCD was induced using in utero electroporation of plasmid containing human mTOR with p.Leu2427Pro mutation. Mice were implanted 4 epidural electrodes and EEG monitored for >2 weeks. Seizures were identified manually. Variance, lag-1 autocorrelation and spatial correlation were computed in 5s bins.
Results: We analyzed 524 pre-ictal periods from 12 mice (300 to 60 s before the seizure onset). Surprisingly, the variance and spatial correlation were not increasing but decreasing (p=0.0059 and p=0.0078, respectively, signed-rank test) with approaching seizure and lag-1 autocorrelation did not show any significant trend. These results suggest rather "critical speeding". In 5 mice we analyzed ultra-slow fluctuations of the markers over >2 weeks. Lag-1 autocorrelation and spatial correlation fluctuations did not show any relationship to seizures. Variance had a mild increasing tendency during periods of high seizure incidence (p=0.18).

Conclusion: In a highly realistic model of FCD, we discovered that the early warning signals of transition to seizure have different character than critical slowing. The results underline the complexity of the dynamics of the epileptic brain.
Supported by grants from the Ministry of Health of the Czech Republic (NU21-08-00533, NU21-04-00601), Czech Science Foundation (GACR 15-08565S, 20-25298S, 18-07908S, 21-17564S) and Primus/23/med/011.

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Influence of reactive oxygen species on epileptiform activity in mice

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Purpose: Reactive oxygen species (ROS) are involved in neuroinflammation processes that facilitate epileptogenesis, characterized by several pathophysiological mechanisms, amongst which neuronal death, synaptic plasticity and neurogenesis. Thus, we hypothesize that changes in ROS disbalance may play a key role in the generation and propagation of epileptiform events on temporal lobe epilepsy (TLE). In this research, the epileptiform activity in mice, induced by Pentylenetetrazole or Kainic Acid (KA), was characterized by classifying the status epilepticus (SE) phases according to the Racine's scale, and applying cellular and molecular techniques.
Method: Adult male C57/BL6 and Knockout gp91phox (NOX2) mice (CEUA 13/2014), 8 weeks-old, weighing 22 - 27 grams, were submitted to an intraperitoneal Pentylenetetrazole injection (80 mg/Kg) or intrahippocampal KA injection (90nM) to induce SE. Pentylenetetrazole-injected mice were placed in beakers for behavior observation and analysis. After 2h or 96h of KA injections, mice were euthanized for cellular & molecular analyses and inflammatory mediators evaluation.
Results: After the induction of SE through Pentylenetetrazole, 73% of C57/BL6 animals died; whereas in NOX2, 47%. The amount of Racine's scale type 5 seizures was reduced in NOX2

animals (Test-t P<0.001). Quantitative analysis of inflammatory mediators on mice's hippocampus was performed 2h and 96h after SE. The concentration in pg/mL of GCSF, VEGF, IL-4, IL-10, IFNy, TNFa, IL-1b, IL-6, IL-17 and IL-13 was modified (Two-way ANOVA P<0.05) in subgroups of C57/BL6 and NOX2 breed. Considering the whole hippocampus, NOX2 and C57/BL6 mice didn't show differences in manual counting of GFAP and IBA-1 positive cells. Preliminary morphometrics analyses currently being carried out in areas of hippocampus show changes to astrocyte cell perimeter and area (Two-way ANOVA P<0.05).
Conclusion: It was demonstrated that high levels of ROS contribute to epileptiform severity in animals due to the release of inflammatory mediators. Complementary studies could bring new insights about treatments and therapies for TLE.

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Acceptability by end-users of a standardized structured format for reporting EEG

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Purpose: The report of the electroencephalogram (EEG) results has traditionally been made using free-text formats with a huge variation in descriptions due to several factors. Recently, the International Federation of Clinical Neurophysiology (IFCN) endorsed the use of the Standardized Computer-based Organized Reporting of EEG (SCORE). This system has many advantages, but only some concerns have been investigated so far. This study aimed to assess the end-users acceptability of this proposed EEG report format.
Method: A 16-item electronic survey was sent to physicians who use EEG services of a medical diagnosis clinic. Physicians had been receiving the EEG reports in free-text formats from the same three board-certified electroencephalographers for the
past three years. In January 2019, the report changed to the SCORE format. The survey assessed five main topics: physician information and historical use of EEG; personal preferences; comparative aspects of the formats; impact of the new format on clinical decision-making; and satisfaction.
Results: Thirty-two of 52 have responded to the survey (61%). On average, 81% of the responders have received enough reports with the new format to reliably complete the survey. Every responder prefers the standardized compared to the free-text format. Twenty-five responders like the inclusion of the head model, and interestingly, five suggest including another legend to differentiate "slow activity" from "other abnormal activity". Virtually all responders would recommend the new format, but one-third read only the conclusion.

Conclusion: Our findings suggest high acceptability of this standardized report format. Despite the limitations of this study, we hope these findings contribute to the improvement and expansion of standardized EEG reporting systems.

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2021 BASED score assessment of electroclinical remission in infantile epileptic spasms syndrome

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Purpose: Defining electrographic remission in Infantile Epileptic Spasms Syndrome (IESS) is challenging as many patients do not have the classical pattern of hypsarrhythmia at the time of diagnosis and, despite neurophysiologists' high confidence in their own assessment, the determination of hypsarrhythmia has poor inter-rater reliability. The 2021 BASED score has been proposed as an EEG grading scale for IESS which ranges from 0 (normal) to 5 (epileptic encephalopathy). Electrographic remission has been defined as pretreatment scores of 4 or 5 improving to ≤3, and pretreatment scores of 3 improving to ≤2.
Aim: To evaluate the 2021 BASED score in a population of children diagnosed with IESS to determine the concordance of clinical and EEG remission established criteria and to compare 2021 BASED scores with previous interpretations.
Method: 15 patients with IESS with pre- and post-treatment EEG registered in our clinic between 2016-2021 were analyzed. 27 patients were excluded because either pre- or post-treatment EEG were lacking.
Results: All pre-treatment EEG were classified as hypsarrhythmia and with a BASED score of 4 or 5. Two patients have achieved clinical remission when post-treatment EEG was registered, reaching a BASED score of 2. Nine patients did not attain neither clinical nor electrical remission. Four patients with EEG remission (post-treatment BASED score 2 or 3) have not reached clinical remission when post-treatment EEG was done.
Conclusion: To our knowledge, our study is the first to apply the 2021 BASED score in a Latin-American population of children with IESS. In our population, it stands out that patients who achieved a BASED score of 2 or 3 post-treatment have not necessarily reached clinical remission.
More studies are need to determine the point of electrical remission.

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Analysis of EEG patterns during ictal seizures by phase amplitude coupling in epilepsy of infancy with migrating focal seizures

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Purpose: It has been reported that the phase amplitude coupling (PAC) is useful for identifying epileptogenic regions and predicting prognosis after focal seizure surgery. In this study, we investigated the usefulness of PAC in the diagnosis of epileptic encephalopathy, Epilepsy of infancy with migrating focal seizures (EIMFS), by calculating PAC during seizure electro encephalogram (EEG).
Method: The subject was a 5-year-old girl with EIMFS who had focal seizures with impaired consciousness and generalized tonic-clonic convulsions on a daily basis since she was 3 months old. The diagnosis of EIMFS was made based on focal shift findings on EEG during seizures. Later, whole exome analysis was performed and *KCNT1* variant was identified. Using a total of six EEGs conducted between 3 and 5 months of age, we calculated the PAC of each electrode at amplitudes of 3-4 Hz in the low frequency phase and 30-90 Hz in the high frequency phase, and statistically analyzed the correlation between the focal shift pattern during seizures and PAC. Focal shift was defined as propagation to the contralateral hemisphere or to non-adjacent electrodes in the ipsilateral hemisphere.
Results: A total of 9 seizures were captured, and the focal shift pattern was 1 ipsilateral and 8 contralateral seizures. There was a significant difference between the electrodes with focal seizure shift and PAC during EEG reading (p<0.001).
Conclusion: The use of PAC to determine focal shift may be useful in the diagnosis of EIMFS. It is necessary to continue to accumulate EIMFS cases and to analyze the correlation among seizure focal shift patterns, causative genes, and epilepsy prognosis.

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The value and limitations of head bobbing in seizure classification

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Purpose: Head bobbing or nodding is characterized by rhythmic anteroposterior head movements and can be seen in a variety of conditions. The purpose of this study was to assess the nature and occurrence of this clinical sign in patients evaluated in the Epilepsy Monitoring Unit in a single institution.
Method: This is a retrospective study. Since 2012, we identified 6 patients with head bobbing after reviewing history and video-EEG monitoring studies of patients admitted to the EMU. All patients underwent phase I monitoring while one patient had additional phase II intracranial monitoring.
Results: Patient 1 is a 27-year-old woman with history of focal and generalized epilepsy with clusters of head bobbing episodes and altered awareness; these were diagnosed as generalized seizures. Patient 2 is a 14-year-old women with global neurodevelopment delay presenting with a one-year history of staring events in association with head bobbing; these were diagnosed as generalized seizures. Patient 3 is a 41-year-old woman with focal epilepsy and

co-existent psychogenic non-epileptic seizures (PNES whose head bobbing episodes were associated with oral automatisms and determined to be epileptic by both scalp video-EEG monitoring (right mesial electrodes) and stereo EEG. Patient 4 is a 20-year-old man with history of intractable generalized epilepsy and head bobbing events diagnosed as generalized seizures. Patient 5 is a 23-year-old woman with focal epilepsy who presented with head bobbing events; these were diagnosed as PNES. Patient 6 is an 8-year-old girl with triple X syndrome and intractable generalized epilepsy whose seizures were associated with head bobbing.
Conclusion: Ictal head nodding can be observed in both children and adults, and is a non-specific sign that can be observed in both epileptic (focal or generalized) and non-epileptic psychogenic seizures. It is important to evaluate patients presenting with this infrequent clinical sign with video-EEG monitoring in order to establish a correct diagnosis.

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The progression of electroclinical features in Lennox-Gastaut syndrome from childhood to adulthood, including interictal and ictal EEG features

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Purpose: To identify how EEG features and seizure types change in LGS patients as they progress to adulthood, to reduce missed diagnoses and facilitate therapeutic measures.
Method: Retrospective, single-centre observational study. 24 patients were recruited. Information was collected on seizure frequency, types of seizures at onset and at last follow-up, and anti-seizure medications (ASMs) used in childhood and at last follow-up. Interictal and ictal findings were identified from paediatric and adult EEG telemetry reports.
Results: The mean age of 24 patients was 28.1 years. 11 patients were female. The commonest seizure type in childhood and adulthood was tonic seizures (TS); atypical absences were more common childhood, and generalised tonic-clonic were more frequent in adults. 16/19 (84.20%) childhood interictal EEGs showed diffuse slow-spike-and-wave (DSSW) activity, 19/19 (100%) showed background slowing (BS), and all childhood sleep EEGs showed diffuse fast rhythms. 8/11 (72.73%) childhood ictal EEGs showed electrodecrement (ED) with fast activity (FA) associated with TS, and 3/11 (27.28%) showed only FA. In contrast, only 7/20 (35%) of adult interictal EEGs showed DSSW; 12/20 (60%) showed BS, but DFR during sleep were present all adult EEGs. DSSW was most commonly replaced by independent multifocal spike discharges (76.92%) in adults. 9/16 (56.25%) adulthood ictal EEGs showed only ED associated with TS, 5/16 (31.25%) showed ED with FA, and 2/16 (12.5%) showed only FA.
Conclusion: Our study highlights that in LGS, both interictal and ictal EEG features change significantly over the lifespan - waking EEG is significantly different in adults, however, sleep EEG features like DFR are retained. This raises issues in adulthood to diagnose LGS because we tra-

ditionally search for the characteristic features described as typical in paediatric patients. Our study stresses the importance of sleep EEGs in adulthood, due to its implications for LGS diagnosis, and subsequent medical management, especially with medicinal cannabis in the UK.

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Relationship between qEEG power spectral density, cognitive impairment and seizure frequency in drug-resistant temporal lobe epilepsy

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Purpose: The aim of this study was to evaluate the relationship between baseline EEG activity using quantitative electroencephalography (qEEG), cognitive performance and clinical characteristics in temporal lobe epilepsy (TLE) patients.
Method: This is a cross-sectional study of adult patients with drug-resistant TLE and controls who underwent EEG. We selected resting-state with eyes-closed samples for qEEG, using the fast Fourier transform approach for the analysis. The mean power spectrum was divided into four frequency bands: delta (1–3.9Hz), theta (4–7.9Hz), alpha (8–12.9Hz) and beta (13–18Hz). Additionally, TLE patients were neuropsychologically tested and cognitive domain scores were calculated combining Z-scores.
Results: Twenty-nine TLE patients (mean age 42±8.2 years; 44.8% women) and 23 age and sex-matched controls were enrolled. Mean epilepsy duration was 14.1±12.6 years. Mild cognitive impairment (MCI) was present in 86.2% (58.6% amnestic). Compared to controls, TLE patients had an increased ipsilateral power band density for theta (p=.045), alpha (p=.023) and beta bands (p=.029) in the anterior region, and an increased delta band (p=.03) in the posterior region. Alpha/theta ratio was lower in the epileptogenic hemisphere, particularly in the posterior quadrant (p=0.013). A higher seizure frequency was correlated with a lower alpha/theta ratio in the ipsilateral posterior quadrant (r:-.425;p=.0219). An increase in all the bands density was directly correlated with amnestic-MCI (p<.005). In the analysis of different cognitive domains separately, executive fluency and verbal memory functions were the ones associated with a higher spectral power density.
Conclusion: qEEG in TLE patients shows an increased power density in all frequency bands in the epileptogenic hemisphere, especially in those with amnestic-MCI. A higher seizure frequency is related with a lower alpha/theta ratio. Power spectral analysis can provide useful information in drug-resistant TLE patients.

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Generalized onset seizures with focal evolution: a case report

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Purpose: Focal clinical features of seizures in idiopathic generalized epilepsy (IGE) can lead to misdiagnosis and inadequate treatment. The need for ictal EEG recording to determine the type of seizures has been stressed in previous studies. Nevertheless, the presence of amplitude asymmetry of generalized interictal epileptiform activity or lateralizing signs during seizure should not be recognized as markers of focal epilepsy.
Method: An 18-year-old man referred to neurologist with recurring seizures. Last year he had 4 bilateral tonic-clonic seizures (BTCS) with no focal features. Myoclonic seizures and absences weren't observed. The patient underwent overnight video-EEG monitoring.
Results: On EEG record, interictal generalized epileptiform activity was present. An epileptic seizure was recorded, beginning with generalized myoclonus, followed by versive right head turn, figure-of-four with right arm extension, and then BTCS. On the EEG record, a generalized polyspike-wave discharge time-locked to myoclonus was seen. Focal seizure pattern in the right frontal region emerged later with subsequent evolution. Brain MRI was unremarkable. Based on history and work-up, the patient was diagnosed with IGE.
Conclusion: Traditional generalized-or-focal dichotomy of epilepsy is imperfect in some cases. Currently, the main theory of pathogenesis in generalized epilepsy is hyperexcitability of neurons leading to immediate involvement of both hemispheres. However, prolonged firing in one of these areas could possibly cause a focal transformation, the localization of which will determine the semiology of seizure. This phenomenon was described as generalized onset seizures with focal evolution (GOFE). This emerging type of seizures in not represented in current classification. Available data together with our case proves that GOFE could be possibly considered in future classifications. Despite the presence of focal features, the approach to IGE patients having GOFE currently is similar to any other IGE.

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The different clinical and electrophysiological effects of cannabidiol-enriched oils on adult patients with drug-resistant epilepsy

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Purpose: Cannabidiol (CBD)-enriched oils are being increasingly used to improve seizure control in adult drug-resistant epilepsy (DRE) patients. We aimed to assess the effects of CBD on seizure frequency and to explore the motor, cognitive, and electrophysiological effects of CBD in responder and non-responder patients to CBD treatment.
Method: We prospectively recruited 19 DRE patients who fulfilled the requirements of the Israeli MOH for medical cannabis treatment and were treated with add-on CBD. Patients were evaluated prior to treatment, and following 4 weeks of titration and 4 weeks of maintenance daily dose of »260mg CBD and »12mg THC. Response to CBD was defined as>50% decrease in debilitating seizures according to weekly seizure diaries. The evaluation included clinical

assessment and EEG recording during rest and evoked potentials (EPs) during visual Go/NoGo task while sitting and walking. Wilcoxon-test was performed to examine the effects of CBD and Mann-Whitney to compare between groups.
Results: Seven patients (43.75%) were responders and nine (56.25%) were non-responders. Responders demonstrated an average *reduction* of 82.4%, while non-responders average *increase* of 30.1% in debilitating seizures. No differences in clinical parameters were found between responders and non-responders to CBD at baseline. However, responders demonstrated larger improvements in sleep quality, MOCA, and HADS anxiety/depression post-treatment. Post-CBD EPs during sitting showed increased P300 amplitude in responders (p=0.046) and decreased in non-responders (p=0.028). During walking, both groups showed a decrease in P300 amplitude (responders: p=0.068, non- responders: p=0.043).
Conclusion: CBD treatment can help reduce debilitating seizures in a subset of DRE patients. No specific motor, cognitive and electrophysiological characteristics can be linked to response to CBD. However, changes in EPs in response to CBD were found between the groups, demonstrating the different effects of CBD on motor and cognitive functions and suggesting promising direction to learn about the differences between responders and non-responders to CBD treatment.

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Automated seizure localization with phase-amplitude coupling in intracranial EEG

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Purpose: Phase amplitude coupling (PAC) identifies dynamic interactions between the phase and amplitude of different frequency bands and has been implicated as a biomarker of epileptic activity. We evaluated the utility of PAC magnitude to identify the ictal onset zone in an automated pipeline using machine learning algorithms.
Method: Eight patients (M:F – 3:5, age – 12.64±8.33 years) with drug-resistant epilepsy underwent intracranial EEG to delineate their ictal onset zone. The invasive electrodes were localized with post-implantation CT and onset channels were identified through visual examination. PAC was computed for a wide range of frequency pairs for low-frequency range of 1-13 Hz and high-frequency range of 14-200Hz. The classification was carried out using support vector machines (SVM), decision trees, k nearest neighbour and naïve Bayes algorithms in both ictal and pre-ictal segments between onset and non-onset channels.
Results: Comodulograms generated from PAC values showed the gamma/ripple-low frequen-

cy coupling to have discriminatory value in ictal onset channels. This was also confirmed by chi-square analysis. In both ictal and pre-ictal segments, SVM showed the greatest testing accuracy of 94.36% and 95.30% followed by the decision tree with 91.91% and 93.42%. Classification potential was comparable in ictal and pre-ictal segments.
Conclusion: PAC can provide valuable assistance in automated seizure marking. Ripple-delta band coupling provides the greatest discrimination between ictal onset and non-onset channels. While no differences in coupling strength were identified in pre-ictal segments using routine hypothesis testing methods, non-linear classification algorithms such as SVM are able to identify ictal onset channels in pre-ictal segments (up to 20 seconds prior to onset) as well.

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Network changes in TLE during an auditory oddball paradigm using magnetoencephalography

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Purpose: Auditory oddball is a paradigm that identifies function across multiple cognitive domains such as attention, working memory etc. Its dysfunction has been well documented in conditions such as temporal lobe epilepsy. We seek to study the network changes in auditory oddball using graph theory and phase amplitude coupling.
Method: Twelve patients with left and right TLE each were considered for this study along with age and gender matched healthy controls. MEG recorded in each condition was subjected to graph theory analysis (clustering coefficient (CC), path length (PL), global efficiency (GE) and small worldness (SW)) and phase amplitude coupling across 5 frequency band and correlated with neuropsychological scores.
Results: Controls showed better performance in neuropsychological tests compared to TLE ($p<0.025$). Both standard and deviant responses showed changes across multiple frequency bands compared to rest. Controls displayed network configuration that was in agreement with small worldness conditions while deviation was observed in both left and right TLE. PAC magnitude was higher in controls ($p<0.001$) in all frequency pairs compared to TLE. TLE showed significant negative correlations with CC and PL with trail making test and positive correlations with SW in the gamma band.
Conclusion: Controls displayed a consistent pattern of activation across all graph theory parameters that was absent in TLE (left and right) and a varying change in PAC magnitude and preferred phase on shifting from standard to deviant stimuli that was absent in TLE.

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Proper timing of an EEG after the first unprovoked seizure helps in predicting sub-

sequent seizures

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Purpose: To evaluate the best time for performing an EEG following the first unprovoked seizure for the purpose of predicting subsequent seizures in the following 24 months.
Method: This retrospective cohort study included 137 children (under 16 years of age) and 65 adults whose EEG test was performed after a first unprovoked seizure. We included those with a follow-up period of at least two years or if a documented second unprovoked seizure has occurred less than two years after the first seizure. We investigated the correlation between the timing and the EEG test results following a first unprovoked seizure within 48 hours (early EEG) and after 48 hours (late EEG) and the occurrence of a second unprovoked seizure.
Results: Of the 202 that had an EEG after their first unprovoked seizure, 105 (52%) had a subsequent seizure within two years, 70 did not, and 27 were lost of follow-up. One-hundred and fifty-six (77%) had an early EEG, 125 (62%) had a late EEG, and 93 (46%) had both an early and a late study. In univariate analysis, we found a statistically significant correlation ($p=0.005$) between epileptiform activity in the late EEG (but not in the early EEG). In the multivariate analysis, we found that epileptiform activity in the late EEG correlated well with a second seizure and that using anti-seizure medication negatively correlated with a second seizure.
Conclusion: EEG performed more than 48 hours after a first unprovoked seizure correlates better with the occurrence of a second seizure within two years than the findings on an EEG performed less than 48 hours after the seizure. This may be used to properly time the performance of an EEG after the first unprovoked seizure.

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Targeted density electrode placement achieves high concordance with traditional high-density EEG for electrical source imaging in epilepsy

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Purpose: High-density electroencephalography (HD-EEG) is increasingly used in presurgical epilepsy evaluation. To overcome its time and resource demand, and thus making it accessible to all epilepsy surgery centers, we evaluated the similarity of EEG source imaging (ESI) solutions when employing a targeted density and a traditional HD-EEG montage.
Method: HD-EEG recordings from consecutive patients undergoing epilepsy presurgical evaluation at the Montreal Neurological Hospital were analyzed. A low-density recording was created by selecting the 25 electrodes of a standard montage from the 83-electrode HD-recording. We then selected the electrode with the highest amplitude interictal epileptiform discharges, and 8-11 supplementary electrodes were added around this electrode. The ESI solution obtained with this EEG montage was compared to the one calculated from the HD-EEG montage using the Euclidean distance between the peak power vertices, their sublobar concordance and a qualitative similarity measure.
Results: Fifty-eight foci of forty-three patients were included. The median distance between the peak power vertices from our targeted density EEG montage compared to the HD-EEG montage was 13.2mm (interquartile range: 7.4-22.8mm), irrespective of the location of the focus, whether temporal or extratemporal (median of 11.6mm, IQR: 7.6-19.2mm; median of 17.5mm, IQR: 0-24.9mm; p=0.58), and hemispheric or in the midline (median of 13.2mm, IQR: 7.8-19.9mm; median of 16.6mm, IQR: 0-24.2mm; p=0.87). Presence of a tangential generator was rare (n=5/58); if present, tangentially oriented foci showed a statistically significant higher distance than radially oriented foci (median of 25.3mm; IQR: 19.2-33.2mm; median of 12.1mm; IQR: 7.3-20.2mm; p=0.04). We found sublobar concordance in 4/58 of the foci (93%). Map similarity was assessed by a board-certified epileptologist, and was given a median score of 4 out of 5, corresponding to a high concordance.
Conclusion: ESI solutions obtained from a targeted density montage show a high concordance with the ones calculated from HD-EEG.

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Exploring graph-derived metrics from functional brain connectivity analyses from PDC and DTF connectomes as VNS outcome predictors

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Purpose: In 1/3 of epilepsy patients, medication may be insufficient, and respective surgery may be offered whenever the seizure onset is localized and situated in a non-eloquent brain region. When surgery is not possible, vagus nerve stimulation (VNS) therapy can be used as an add-on treatment to reduce seizure frequency and/or duration. However, screening tools

or methods for predicting patient response to VNS and avoiding unnecessary implantation of VNS in non-responders (NR) are unavailable, and confident biomarkers of clinical efficacy are unclear. This study aims to identify graph-derived measurements from functional brain connectivity analyses that may be used as new VNS outcome predictors.
Method: Thirty-seven refractory epilepsy patients were retrospectively studied, calculating five functional brain connectivity indexes (Global Efficiency, Average Clustering Coefficient, Modularity, Global Reaching Centrality, and Degree Assortativity) per frequency band (Delta, Theta, Alpha, Beta, and Broadband) upon partial directed coherence (PDC) and direct transform function (DTF) connectivity matrices from EEG recordings. Data were separated into awake and sleep conditions, where ten epochs of 10 seconds were selected from the resting state awake condition and non-rem sleep stage II. Graph measurements were calculated upon three thresholding methods: non-thresholded, surrogate data test, and thresholded binarized connectomes.
Results: We found some graph measures from the PDC connectome were statistically different between responders (R) and non-responders (NR) using the Mann-Whitney U test with Benjamini-Hochberg correction procedure and a false discovery rate of 5% ($p<0.05$). Specifically, global efficiency and average clustering coefficient in beta/broadband and delta/broadband, respectively, during non-rem sleep stage II had a higher value in non-responders. Also, the modularity on the alpha band in the wakefulness state had lower values in non-responders.
Conclusion: Our study showed that global efficiency, average clustering coefficient, and modularity calculated from PDC connectomes might discriminate between R and NR based on EEG analysis before VNS implantation.

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The potential effect of sleep circadian rhythm in the detection of epileptiform discharges in epilepsy

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Purpose: The sleep-wake cycle and the emergence of interictal epileptiform discharges (IEDs) in electroencephalogram (EEG) share a close association in epilepsies. Recent studies have shown that sleep onset and offset are significant triggers for the generation of IEDs. We aimed to investigate the impact of nocturnal sleep on the presence of IEDs in a small case series of patients with a first unprovoked generalized seizure.
Method: We included 16 patients (mean age 26yo, 71% female) with a first unprovoked generalized seizure who underwent a full-night 12-hour ambulatory (AEEG) (from 9:00 pm to 9:00 am). All these patients already had a previous normal 1-hour sleep-deprived EEG (awake to N2-sleep). The spike index (SI) was calculated for the first (first-hr-S) and last hour of sleep

(last-hr-S) and for the first hour after awakening (first-hr-W).
Results: Ten patients (62.5%) presented IEDs during the AEEG. Eight patients presented generalized and two presented focal epileptiform discharges. The SI was greater during the first hour of sleep than the rest of the segments (first-hr-S > last-hr-S > first-hr-W). This pattern was only observed in patients with generalized IEDs. In those with focal IEDs, the SI was equally distributed in non-REM stages during the whole night.
Conclusion: Despite several potential confounders, our results support the hypothesis that the sleep circadian rhythm has more influence on IEDs than the sleep-awake boundaries itself. Therefore, a full-night AEEG may be an alternative to a sleep-deprived EEG, at least in young people with a first unprovoked generalized seizure.

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Differential EEG findings depending on type of praxis in reflex epilepsy

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Purpose: Among reflex epilepsies, praxis induced epilepsy (PIE) has long been associated with juvenile myoclonic epilepsy (JME). However, the ILAE epilepsy classification in 2017 and epilepsy syndrome in 2022 determined stringent definition of JME . We present a case of PIE who showed change in EEG interictal discharges according to the type of praxis.
Method: A 32-year-old male with medically intractable seizures, despite a tentative diagnosis of JME and treatment with valproic acid (VPA) and carbamazepine (CBZ), was investigated. Seizure semiology, precipitating factors, and data on long-term video EEG monitoring lasting three days were analyzed.
Results: His seizure semiology was symmetric myoclonic jerks of the upper limbs evolving to generalized convulsion, which seemed generalized myoclonic seizures. His seizures were triggered by stacking-type puzzle games such as Tetris, building-type games such as Minecraft, and assembling building blocks. Three-dimensional environments more easily triggered seizures than two-dimensional (2D) ones did. Interictal EEG showed focal spikes maximum in the right frontal area at rest, but epileptiform discharges distributed in the left hemisphere while playing 2D Tetris. While he was assembling building blocks, hemispheric spikes were observed on the right or left hemispheres independently as well as bilateral synchronized polyspikes. Ictal EEG showed 1.5 Hz polyspikes arising from the right frontal area. Brain MRI was unremarkable. Thus, he was diagnosed as combined generalized and focal epilepsy. Increased doses of VPA and CBZ and add-on therapy with gabapentin achieved seizure-free for more than 1 year.
Conclusion: Differential susceptibility of cortical regions within specific neural networks, which are involved to certain types of praxis, can be objectively assessed by EEG findings and important to determine seizure onset zones or networks in PIE. In patients with medically intractable PIE, combined generalized and focal epilepsy should be considered instead of JME,

even though their semiology suggests generalized onset seizures.

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Functional connectivity alterations in patients with post-stroke epilepsy based on source-level EEG and graph theory

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Purpose: We investigated the differences in functional connectivity based on the source-level electroencephalography (EEG) analysis between stroke patients with and without post-stroke epilepsy (PSE).
Method: Thirty stroke patients with PSE and 35 stroke patients without PSE were enrolled. EEG was conducted during a resting state period. We used a Brainstorm program for source estimation and the connectivity matrix. Data were processed according to EEG frequency bands. We used a BRAPH program to apply a graph theoretical analysis.
Results: In the beta band, radius and diameter were increased in patients with PSE than in those without PSE (2.699 vs. 2.579, p=0.003; 2.261 vs. 2.171, p=0.003). In the low gamma band, radius was increased in patients with PSE than in those without PSE (2.808 vs. 2.617, p=0.004). In the high gamma band, the radius, diameter, eccentricity, and characteristic path length were increased (1.828 vs. 1.559, p=0.001; 2.653 vs. 2.306, p=0.002; 2.212 vs. 1.913, p=0.001; 1.425 vs. 1.286, p=0.002), whereas average strength, global efficiency, local efficiency, mean clustering coefficient, and transitivity were decreased in patients with PSE than in those without PSE (49.955 vs. 55.055, p=0.001; 0.756 vs. 0.827, p=0.001; 4.795 vs. 5.741, p=0.002; 0.727 vs. 0.810, p=0.001; 1.091 vs. 1.215, p=0.001). However, in the delta, theta, and alpha bands, none of the functional connectivity measures were different between groups.
Conclusion: We demonstrated significant alterations of functional connectivity in patients with PSE, who have decreased segregation and integration in brain network, compared to those without PSE.

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Effects of Cenobamate therapy on EEG connectivity, seizures and cognitive performance in people with drug resistant epilepsy

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Purpose: Epilepsy is a neural network disorder. Quantitative EEG offers innovative parameters estimating cortical connectivity, that recently was suggested as a possible therapeutic biomarker in epilepsy.Cenobamate (CNB) is a newly approved anti-seizure medication in people with epilepsy.
The aim of the present study is to study the modulation of EEG connectivity induced by Cenobamate and its correlation with clinical outcomes.
Method: We enrolled 18 people with drug resistant epilepsy (DRE,8 females, 47±16-year-old) and twenty-five healthy controls (HC,12 females, 51±18-year-old HC). Two DRE people dropped out. Sixteen DRE people underwent 19-channel EEG before (T0) and after 6 months (T1) of CNB therapy.Power spectral density (PSD) and phase Locking Value (PLV) for delta, theta, alpha, beta and gamma frequency bands were calculated. Cognitive performance was evaluated by Epitrack test. Seizure frequency was collected.
Results: After CNB, 11/16 DRE (69%) people were responders (>50% seizure frequency reduction) and 2 of them were seizure free (12%). At T0 and T1, alpha, beta and gamma PSD was lower, while delta and theta PSD was higher in DRE people than in HC ($p<0.001$).
At T0, alpha PLV was lower in DRE people than in HC ($p<0.001$), while, at T1, PLV of DRE group was lower than HC in all frequency bands except of delta ($p\leq0.006$). A nearly significant amelioration of Epitrack scores were detected at T1 ($p=0.073$). We did not find any significant interaction of band*Time in DRE group.
Reduction of PLV significantly correlated with seizure reduction (%) in all frequency bands except of alpha ($p=0.39$-0.004) and with CNB plasmatic level ($p=0.031$-0.001).
Conclusion: Reduction of EEG connectivity after CNB is highly correlated with clinical outcome and corroborates the potential role of EEG connectivity as a good therapeutic response biomarker in people with epilepsy.Cenobamate is an efficacious drug choice for DRE people without impacting on their cognitive performance.

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Relationship between cortical tuber MRI subtypes and interictal discharges in tuberous sclerosis complex: a scalp EEG study

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Purpose: The epileptogenicity of certain cortical tubers in Tuberous Sclerosis Complex (TSC) as classified by MRI has been previously investigated using stereo-electroencephalography; however, the association between tuber subtypes and interictal epileptiform discharges (IEDs) as detected by scalp EEG remains unclear. The aim of this study is to investigate this relationship to clarify the degree of cortical irritability of each tuber subtype.
Method: A retrospective analysis TSC cases, who underwent both MRI and scalp EEG, was performed. Cortical tuber subtypes were classified based on previously reported methods, with Type A being defined as T1 and FLAIR high signal, Type B as T1 low signal and FLAIR high signal, and Type C as Type B with associated mass effect (Gallagher, et al. 2010). IEDs were evaluated using both automatic detection with Persyst14 software and visual inspection, with discharges occurring at a rate of 10 or more per 30 minutes being considered positive. The presence of IED and the number of subtypes of lesions were examined in each of the left and right frontal, temporal, parietal, and occipital lobes, and the number of subtypes of lesions was compared in relation to the presence of IED in each region.
Results: The analysis included 23 cases, with a mean age of 28 years. 21 cases had a history of seizures, with 7 cases of focal seizures. A total of 87, 37, and 76 cortical tubers were classified as Type A, Type B, and Type C, respectively. 9, 4, and 48 tubers of Type A, B, and C were found in IED positive lesion, respectively, with prevalence of Type C significantly higher than other tuber subtypes (p <0.001).
Conclusion: In the cerebral lobes where positive IEDs were detected by scalp EEG, a high prevalence of Type C tubers was observed, implicating its higher cortical irritability.

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Correlation between intraoperative EEG findings from the hippocampus and amygdala and postoperative outcomes in patients with medial temporal lobe epilepsy

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Purpose: To determine whether intraoperative findings from the hippocampus and amygdala correlate with clinical features and postoperative outcomes in patients with medial temporal lobe epilepsy (MTLE).
Method: This study included 36 patients with non-lesional and unilateral MTLE who underwent anterior temporal lobectomies with amygdalohippocampectomies at our hospital, from April 2013 to March 2021. We intraoperatively measured EEG recordings from the surface of the hippocampus and amygdala for three minutes. According to the number of spikes during EEG recordings, patients were divided into two groups; those with (group A) and without

(group B) more spikes from the amygdala than from the hippocampus. We automatically measured hippocampus and amygdala volumes based on preoperative magnetic MRIs, and the volume ratio was calculated from the affected/unaffected sides. The postoperative seizure outcomes were classified into two groups: good, International League Against Epilepsy (ILAE) class 1; poor, ILAE classes 2-6.
Results: Regarding intraoperative EEG findings, 13 of the 36 patients (36.1%) were assigned into group A and the others to group B. Twenty-five patients (69.4%) had good outcomes. Seizure outcomes in group A were significantly poorer than those in group B (group A: 8 patients (61.5%); group B: 3 patients (13.0%), $p < 0.005$). The number of spikes from the hippocampus did not correlate with hippocampus volume ratios, whereas the number of spikes from the amygdala significantly correlated with amygdala volume ratios ($p=0.003$, $R=0.476$).
Conclusion: In patients with MTLE, more spikes recorded from the amygdala than from the hippocampus significantly correlated with poorer outcomes. Moreover, a positive correlation between the number of spikes from the amygdala and the amygdala volume ratio was observed preoperatively. These results clarify the relation between the hippocampus and amygdala in MTLE, regarding the origin and propagation of epileptogenesis, and will help improve postoperative prognosis.

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Quantitative analysis of visually-normal EEG reveals spectral power abnormalities in temporal lobe epilepsy

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Purpose: Aim of this work was to perform quantitative spectral analysis of the visually-normal electroencephalographic signal (EEG), and to compare these parameters in patients with temporal lobe epilepsy (TLE) and healthy controls (HC).
Method: We analyzed EEG recordings from 22 TLE and 22 HC. From each recording, 20 seconds were selected with the following criteria: visually-normal signal (absence of spikes), no artifacts, no physiological noise. Power spectral density with the periodogram method was calculated using Matlab in-house software. For each patient, we calculated total power of all frequency bands, as well as whole-brain alpha-theta (ATR) and alpha-delta ratios (ADR). Subsequently, we also calculated the same indices for the anterior and posterior zone. Finally, for TLE patients, ATR and ADR ipsilateral and contralateral to the epileptogenic focus were calculated. Statistical t-tests were applied to spectral parameters between two groups. Significance threshold was set at $p<0.05$.
Results: In all comparisons, ATR and ADR were significantly decreased in TLE patients com-

pared to HC. In particular, statistically significant differences were observed between ipsilateral anterior, ipsilateral and contralateral posterior quadrants for ADR ratio; ipsilateral and contralateral posterior quadrants and ipsilateral temporal region for ATR ratio. In all regions, total power of frequency bands was decreased bilaterally in TLE compared to HC. Comparing ipsilateral and contralateral regions in TLE patients only, ratio values were lower in ipsilateral zone than in contralateral zone, while no differences were observed for power values of frequency bands.
Conclusion: This study confirms that the power spectrum of qEEG is shifted towards lower frequencies in TLE patients, in particular in the ipsilateral zone. Of note, our results were found in visually normal recordings, providing further evidence of the potential value of qEEG in the diagnosis and evaluation of TLE.

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EEG-based encephalopathy grading: an inter-rater reliability study

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Purpose: The VE-CAM-S (Visual EEG Confusion Assessment Method – Severity) scale quantifies encephalopathy severity based on visually-identified EEG features. We designed an inter-rater reliability study to investigate expert agreement in assessing encephalopathy severity using the VE-CAM-S grading system.
Method: We created an online test with thirty-two 15-second EEG samples. Each question asked users to indicate presence/absence for each of 29 EEG features relevant to grading encephalopathy, 11 of which were used in the VE-CAM-S. Gold standard was based on the consensus of 3 authors (IS, FN, MBW). Ten experts from 6 institutions participated. We quantified performance by average Spearman correlation of VE-CAM-S scores with the gold standard, and average sensitivity/specificity. We performed a qualitative analysis to identify errors in recognizing EEG features that most affected VE-CAM-S scores.
Results: The average [95%CI] correlation between VE-CAM-S scores with the gold standard was 0.73 [0.59-0.86]. Specificity was very high (>90%) for all but generalized delta (77%). Sensitivity was high (>70%) for all but brief generalized attenuations (69%), generalized periodic discharges (67%), generalized theta (63%), brief potentially ictal rhythmic discharges (BIRDs) (57%), generalized alpha (57%), generalized beta (50%), and extreme delta brush (EDB) (50%). Probable reasons for errors were subtlety of some findings; confusing some findings (e.g., generalized beta vs. myogenic artifact, burst suppression vs. brief generalized attenuations); failure to correctly recognize BIRDs (mislabeled as focal interictal epileptiform discharges) and EDB (mislabeled as generalized rhythmic delta activity). The largest errors occurred when

experts missed or falsely identified features that carry higher weight in the VE-CAM-S scoring rubric.
Conclusion: Expert agreement in VE-CAM-S scoring is high. Error analysis identified several ways to improve future versions, including breaking high-stakes features into smaller parts; creating a "cheat sheet" with scored examples to allow scorers to choose the closest match; and designing teaching materials to help scorers recognize subtle variations of high-stakes patterns.

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Novices and experienced EEG readers can be differentiated by a competency-based e-examination of routine EEG interpretation

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Purpose: To develop an assessment tool for evaluation of competence in routine electroencephalography (rEEG) interpretation.
Method: An online, anonymous rEEG examination was developed. A previously published curriculum map was used to design 30 single-best-answer multiple choice questions covering four EEG domains: normal, abnormal, normal variants, and artifacts. Each question contained an EEG image displayed in two montages (bipolar and average). Questions were pre-reviewed, modified, and correct answers adjudicated by EEG experts (FAN/RF/SR/WT/SB). Respondents reported their level of confidence (LOC, 5-point scale) with answering questions in each domain. Accuracy and item discrimination were calculated for each question, and LOC for each domain. The test was disseminated by the ILAE and shared on social media.
Results: Of 2,076 responses, 922 were complete. Respondents comprised medical students, neurology residents, EEG/epilepsy fellows, neurology and non-neurology attending physicians, neurophysiologists/epileptologists (experts), technologists, and others. Mean accuracy [95%CI] was 74.4% [73.4-74.4]. Accuracy and LOC correlated with level of experience: experts had highest mean accuracy and LOC; neurology residents performed significantly lower than experts ($p=0.002$) and fellows ($p<0.001$), and were significantly less confident than experts and fellows in all 4 domains (all $p<0.001$). Accuracy was similar for fellows and experts, fellows had lower overall LOC. Among neurology residents, accuracy and LOC correlated with the number of prior weeks of EEG rotation. Accuracy increased progressively from 64% (0 prior EEG weeks) to 75% (>12 prior weeks). All but 3 questions had discrimination index of >0.25.
Conclusion: This competency-based rEEG examination maps to a published EEG curriculum, stratified performance by level of prior training, and had excellent overall psychometrics. This

examination could support competency-based assessment of EEG interpretation.

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Monitoring faciobrachial dystonic seizures with wearable devices using machine learning

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Purpose: Patients' self-reported seizure records are used to guide treatment and inform regulatory approvals of medications and other therapies; however, these subjective seizure records have been shown to be inaccurate. In particular, LGI1 autoimmune faciobrachial dystonic seizures (FBDS) can be difficult to diagnose, and may be confused with other etiologies. Wrist-worn wearable devices capable of measuring physiological and accelerometry signals, have found success in providing more objective measurements for non-invasive monitoring of generalized tonic-clonic seizures and may prove useful for identifying FBDS.
Method: Two LGI1-IgG seropositive patients and four control subjects, wearing Empatica E4 devices, were recruited for this study. Two eight-hour sleep periods of each patient: pre- and post-treatment, were recorded. An algorithm was developed based on accelerometry (ACC) signals to detect events of interest. After event identification, we calculated the ACC magnitude, duration, and electrodermal activity (EDA) characteristics of detected events.
To better identify these events, we are developing a multi-task deep-learning model capable of learning multiple types of seizures simultaneously. The flexible parameter sharing inherent to these models allows knowledge gained from identifying Seizure Type A to be utilized when classifying Seizure Type B, and vice versa, thereby improving the accuracy when classifying both types of seizures.
Results: Preliminary results demonstrated successful monitoring of FBDS in these patients and recruitment of additional patients is ongoing. We are incorporating 174 patients from the My Seizure Gauge trial to compile a dataset featuring patients with a variety of seizure types to train our model to identify and classify motor, GTC, myoclonic, dystonic, subclinical, clonic, tonic, and dyscognitive seizures.
Conclusion: Identifying FBDS seizures with a wrist-worn device is feasible. Multitask deep learning models may improve the accuracy of identifying and classifying a variety of seizures, resulting in a tool which will provide objective measurements for treatment guidance and clinical decisions.

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An audit of EEG requests to an Irish tertiary hospital neurophysiology department

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Purpose: EEG is a valuable tool in the diagnosis of epilepsy, however only when used appropriately. To allow for effective utilisation of this limited resource, it is imperative that referrals have a clear indication. The department in St. James's Hospital Dublin accepts referrals for in-patients and outpatients publicly funded through the Health Service Executive (HSE Ireland). We aimed to evaluate EEG requests and determine if the indication fulfils the guidelines published by the National Institute for Healthcare and Excellence (NICE).
Method: We conducted a retrospective review of 277 consecutive EEG referrals for 257 adult patients. All patients who had an EEG between January 1st, 2022 and May 16th, 2022 were identified. Referral indications were compared to the NICE guideline which states: "*An EEG should be performed only to support a diagnosis of epilepsy in adults in whom the clinical history suggests that the seizure is likely to be epileptic in origin*."
Results: 32% of requests (n=90) did not meet the NICE guidelines for EEG requests. 56% of EEGs revealed an abnormality, with 18% of all studies displaying an epileptiform discharge. Among EEG with epileptiform discharge, 90% of referrals were considered appropriate. When the NICE criteria was met, an epileptiform discharge was identified in 22% of cases. When not fulfilled, 7% of EEGs revealed an epileptiform abnormality. Mean wait time for outpatient EEG was 71 days.
Conclusion: Inappropriate EEG requests represented a significant portion of performed EEGs in our institution. This places an additional burden on the service and may contribute to delays in diagnosis. Appropriate requests were more likely to reveal a liability to seizure. This audit underscores the need for ongoing education across speciality teams to promote published guidelines in an attempt to improve efficiency of services.

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Clinical utility of intraoperative electrocorticography in epilepsy surgery; analysis of fifteen focal epilepsy or encephalopathy surgical cases

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Purpose: We aim to determine the clinical utility of intraoperative electrocorticography (iECoG) in our series of patients who underwent epilepsy surgery.
Method: Clinical data, iECoG, pathology and outcome of 15 patients who underwent epilepsy

surgery with iECoG at our centre were reviewed.
Results: Our series included 6 female and 9 male patients, ranging from 3 to 48 years of age. Epilepsy evolution time was 1 to 32 years with a mean duration of 10 years. Twelve patients suffered from focal epilepsy and three presented epileptic and developmental encephalopathy (EDE). Pathological analysis revealed 6 patients with malformation of cortical development (MCD) Type II, 1 cavernoma, 2 ganglioglioma, 1 meningioma, 1 craniopharyngioma, 2 encephalocele and 2 patients with mild malformation of cortical development with oligodendroglial hyperplasia (MOGHE).
The electrographic patterns registered by iECoG were very high amplitude spikes and polyspikes/diffuse paroxysmal fast activity in patients with EDE, repetitive spikes and polyspikes in patients with MCD Type II and encephalocele and less frequent repetitive spikes or sharp waves in patients with gliosis and tumours.
The Engel´s classification of postoperative outcome was Ia in 10 patients, IIa in one patient with meningioma, IIIa in three patients (EDE (2) and MCD Type IIB (1)), and IVa in a patient with craniopharyngioma, who had a left frontal neocortical resection.
During surgery, based on the specific iECoG findings we proposed extending the resection in 13 (86,6%) patients. Resection was finally extended in 11 patients, and 9 of these patients presented an Engel Ia outcome. In the rest of the cases where the resection could not be extended, outcomes were Engel Ia, IIa, IIIa and IVa.
Conclusion: Taking into account the results of our series, we consider iECoG as a useful tool in epilepsy surgery in order to guide the extension of the resection, which is favourably related to seizure outcome.

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Spike detection and electric source imaging (ESI) to study epileptogenic networks during presurgical evaluation

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Purpose: Over 30 % of people with focal epilepsy are drug-resistant and can only be cured by surgically removing the epileptogenic tissue. In the majority of patients with focal epilepsy, non-invasive diagnostic procedures help to identify the region to be surgically resected (Engel 1981). Here, we investigated the potential added value of computer-assisted interictal spike detection and Electric Source Imaging (ESI).
Method: Electrical source imaging (ESI) is increasingly used in preoperative assessment. High-density EEG (HD-EEG) ESI has been shown to provide an additional diagnostic value compared to standard low-density EEG (LD-EEG). Epilog's Persyst EEG analysis software was used for supervised automatic spike detection and ESI. Source visualization was then based on the individual head model (3D MRI), and ESI results were integrated with other modalities, including MRI, MAP, PET, and SPECT, for preoperative SEEG planning. We compared ESI results

from 80 patients with high-density EEG recordings (256ch) with normal scalp EEG from 30 retrospective MRI-positive cases eligible for epilepsy surgery and 25 consecutive patients, including MRI-negative cases.
Results: The distribution of spike sources in the retrospective group showed individual variability specific to the lesion site. This information was used in the prospective evaluation considering the MRI-negative cases. In most cases, ESI clusters correlated with other modalities (semiology, MRI, MAP, PET, SPECT) that supported localization of the epileptogenic focus. The most frequent ESI clusters were located in the Hippocampus.
Conclusion: HD EEG had a better spatial resolution of ESI compared with standard scalp EEG. In the presurgical assessment, ESI analysis showed good complementary value and can improve the localization of seizure onset in patients with negative MRI findings.

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EEG synchronization measures as a predictive biomarker of VNS response in drug-resistant epilepsy: a retrospective study

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Purpose: Currently, there are no predictive biomarkers for the efficacy of Vagus Nerve Stimulation (VNS). Neural desynchronization is a key mechanism of VNS action, and electroencephalogram (EEG) synchronization measures may be explored as possible predictive biomarkers of clinical efficacy. In addition, during sleep, a higher level of brain synchronization has been reported and interictal epileptiform discharges are known to be more frequent. This study aims to explore and compare EEG synchronization metrics during sleep and wakefulness extracted before VNS implantation, between Responders (R) and Non-Responders (NR).
Method: The Weighted Phase Lag Index (wPLI) was computed based on preimplantation EEG in 38 Drug-Resistant Epilepsy (DRE) patients (24 NR, 14R) in wakefulness and stage 2 of NREM sleep. Two-sample t-tests were conducted to compare the wPLI between R and NR and EEG states. Finally, a linear mixed model using the wPLI as the dependent variable was fitted, using EEG states, response to the therapy, epilepsy duration, age, sex, antiseizure-medication (ASM), and benzodiazepine intakes as covariates.
Results: In all patients, a higher wPLI in the delta band was observed in wakefulness com-

pared to sleep (p=0.004). This difference in the delta band remains significant in the NR group (p=0.015) but not in the R group (p=0.6). Moreover, in sleep only, a higher alpha wPLI was found in NR compared to R (p=0.01), which remained significant after controlling for all covariates (p=0.036).
Conclusion: Future NR may show stronger brain synchronization during wakefulness and sleep in delta and alpha bands compared to R. EEG synchronization measures could give interesting insights into VNS response before the implantation.

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Increased source-reconstructed functional connectivity in adults after a first unprovoked seizure.

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Purpose: Approximately ten percent of the population will experience at least one epileptic seizure in their life. Depending on individual factors, there is up to 50% recurrence risk. Patients diagnosed with epilepsy have increased connectivity and power in comparison to healthy controls (Li Hegner et al. Brain Topography 2018; *31*(5), 863–874). Therefore, we evaluated if patients after a first unprovoked seizure would have increased functional connectivity and power compared to healthy controls. Also, we investigated if there were differences between the brain network of patients after a first seizure and those with established epilepsy.
Method: We retrospectively selected patients that had a first unprovoked seizure and a routine resting-state EEG (rs-EEG) available. Patients that did not develop epilepsy at least six months after the first seizure were considered non-epileptic. We analyzed 5 minutes of rs-EEG data of non-epileptic patients (n=19), age and sex-matched epileptic patients (n=19), and healthy controls (n=19). We computed source-reconstructed power and the imaginary part of coherency (imCoh) in six frequency bands (1-40 Hz). Group differences were assessed using permutation analysis of linear models.
Results: Patients with epilepsy had higher imCoh in the theta frequency band in contrast to controls. The increase was in temporo-occipital (pFWE=0.026, d=0.87) and parieto-occipital regions (pFWE=0.028, d=0.83). Similarly, the non-epileptic group, in comparison to controls, showed increased imCoh in the theta band in temporo-occipital (pFWE=0.35, d=0.85) and parieto-occipital (pFWE=0.28, d=0.87). This group also had decreased imCoh in the beta1 band in the fronto-central (pFWE=0.021, d=0.74) and temporo-occipital (pFWE=0.02, d=0.67) regions. There were no significant differences in imCoh nor power between the epileptic patients and the non-epileptic group.
Conclusion: Routine EEG detected increased functional connectivity in patients that just had a first seizure, providing new insights into the early changes in the brain's network near the time of a first unprovoked seizure.

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Detrended fluctuation analysis in the presurgical evaluation of epilepsy patients

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Purpose: Epilepsy surgery is considered for selected patients with refractory epilepsy. Meticulous presurgical planning is essential for successful surgery, yet current methods are often inadequate for the unambiguous identification of the epileptogenic zone (EZ). Local cortical excitation/inhibition balance is reflected in long-range temporal correlations (LRTC) of neuronal oscillations, which could provide a novel tool for EZ localization. This study aims to determine the utility of LRTC in the presurgical workup.
Method: 62 patients who had undergone stereoelectroencephalography (SEEG) for presurgical evaluation and had presurgical MEG recordings were selected. We evaluated LRTCs with detrended fluctuation analysis (DFA) of source-level interictal MEG data and estimated the DFA scaling exponents for cortical parcels. Five experienced neurophysiologists individually compared the resulting DFA maps to the preimplantation hypotheses. Each hypothesis was marked as concordant or discordant with the DFA maps. The hypotheses were compared to a two-year surgical outcome. A hypothesis was designated as True if resection within this hypothesis resulted in ILAE II or better. A hypothesis was designated as False if there was no resection within it or if resection resulted in a worse than ILAE II outcome. If DFA was concordant with True hypothesis, this was marked as a true positive.
Results: Preliminary results from a subset of 8 patients (to be excluded from the study) show a sensitivity of 80.0% (51.9% - 95.7%, 95% Clopper-Pearson Exact Confidence Interval) and a specificity of 73.3% (63.0% - 82.1%). Interrater agreement (Krippendorf's alpha) among patients with ILAE II or better was 0.62, and 0.59 among the rest. The overall interrater agreement was 0.60. Additionally, 75% of patients analyzed had high DFA areas that were not targeted for SEEG implantation.
Conclusion: DFA is a novel noninvasive method for localizing seizure onset zone that can be utilized similarly to radiological images in the presurgical evaluation of epilepsy.

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EEG alterations after chronic MDMA use – a retrospective cohort study

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Purpose: MDMA-associated neurotoxic effects and long-term prognosis in chronic, intensive users have been a focus of interest. In this study, we aimed to observe EEG activity changes that develop in the context of the upper-mentioned substance use.
Method: The study was conducted in the Central University Clinic Named After Acad. N.Kipshidze. Written consent was obtained from all patients. EEGs of 30 chronic MDMA users were analyzed and compared to 30 individuals who did not report any kind of substance abuse. None of the patients had underlying neurologic illnesses. The two groups exhibited the same demographic distribution.
Results: The mean age of the MDMA users was 24.7 years (SD=+/- 3), same variable in the other group being 25.1 years (SD= +/-2.7). Both groups had equal gender distribution. Mean duration of MDMA use was 23 months (SD=+/-7). The mean frequency of drug abuse based on patients' reports was once in 2.3 weeks. None of the patients from the first group reported being in a sustained remission, with mean abstinence being 2.9 weeks. The biggest increase in the difference between the EEG patterns if the two groups were evident in the 8-11 hz range, being consistent with alpha activity. The most prominent spectral power difference was observed at 10.5 hz: mean power in MDMA abusers 11 μV^2 (SD=+/-1.1), same value in unexposed individuals 4.5 μV^2 (SD=+/-1.5).
Conclusion: Chronic, frequent MDMA use seems to significantly alter baseline alpha activity. Given the important role of alpha activity in cognitive functioning, mood state, stress reduction and overall productivity of mental activity, it is relevant to stress the possible influence of MDMA use on this functions and long-term risk of cognitive decline or mental illness development.

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Validation of a machine learning algorithm for the prediction of first anti-seizure medication response in focal epilepsy: a multicenter cross-sectional study

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Purpose: For people with epilepsy, the EEG is a pivotal neurophysiological technique for confirming the diagnosis and guiding clinical management. However, no definite EEG prognostic biomarkers for anti-seizure medications' (ASMs) efficacy have been defined. The purpose of this study is to use a machine-learning (ML) approach to determine the predictive power of

conventional scalp EEG for seizure freedom in a population of newly diagnosed focal epilepsy patients after a first ASM initiation. We hypothesize that quantitative EEG features can predict clinical outcome (seizure freedom) before ASM initiation.
Method: We have examined 205 newly-diagnosed patients with focal epilepsy from six epilepsy centers across Italy between March 2018 and January 2022. We dichotomized clinical outcomes into seizure-free (SF) and non-seizure-free (NSF) after one year of ASM initiation. We built a cross-validated data-driven model based on two different ML models: Convolutional Neural Network and Partial Least Squares regression. We then performed a K-fold cross-validation procedure to assess the generalization of our model in predicting clinical outcome using one center as the test set and the remaining five centers as the training sets.
Results: A total of 152 features were extracted from the conventional 19-channel EEG recordings. The most common ASMs employed in our cohort were LEV (61%) and LTG (17%). The ML model was able to predict seizure freedom with an area under the curve (AUC) of 0.75 using the EEG performed before ASM initiation (T0). The ML model used on an independent EEG dataset (test set) achieved a prognostic prediction with an AUC of 0.77.
Conclusion: This study provides an ML algorithm for predicting the clinical response to ASMs in people with epilepsy. Future studies may benefit from the pipeline proposed in this study for the development of a clinical decision-making tool for data-driven, individualized ASM choices for people with epilepsy.

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The long-term outcomes of patients with a negative prolonged ambulatory EEG monitoring: a cross-sectional follow-up study

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Purpose: Ambulatory electroencephalography (AEEG) recording is a technique of continuous EEG recording. It seeks to capture inter-ictal epileptiform activity or paroxysmal events when the patients are in their natural setting, outside the controlled environment of the hospital, to provide a clinical diagnosis. (Seneviratne U et al., Handb Clin Neurol. 2019;160:161–70.). This study aimed to describe long-term outcomes among a cohort of patients with no events or interictal abnormalities on AEEG tests at the time of assessment and identify factors associated with quality of life and epilepsy diagnosis.
Method: This cross-sectional telephone follow-up study was conducted in June-November 2021 at the Neurology Department in a metropolitan hospital in Sydney, Australia.
Results: Forty-seven of 105 eligible (45%) participants were enrolled. Twenty-one (45%) participants had been diagnosed with epilepsy by a 12-year follow-up. Taking anti-seizure

medication, having experienced a seizure event, and having marriage and education-related characteristics were associated with an epilepsy diagnosis. Physical QOL was found to be associated with age, employment status and history of experience of a seizure event. QOL and an epilepsy diagnosis were not shown to be statistically related.
Conclusion: Nearly half of the participants received an epilepsy diagnosis at long-term follow-up, despite having tested negative on AEEG tests at the time of assessment. Prolonged AEEG testing is an essential tool to aid the diagnostic process. Clinical examination, including accurate history taking, is as critical in establishing a diagnosis of epilepsy as electrophysiologic assessment.

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An alternative to collodion

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Purpose: Improve Electrode application for Long-term EEG/Video monitoring without using Collodion.
Method: Prepare the skin as usual. Cut gauze into one inch by one-inch squares. Fill a 10 mm electrode cup with a conductive paste (Ten-20 conductive paste or Elifex, just enough to fill the cup. Squeeze a bit of cream (EC2 genuine Grass electrode cream) on a piece of gauze to hold the electrode down for about 10 seconds, which dries up fast. This method does not actually “mix” conductors, since there is almost no contact between the two. One conductor is inside and the other one is outside and not serving any conducting function. The electrode impedance should be less than 5.000 Ohms and balanced. Mixeopoew tm Microporus Hypo-Allergenic Surgical tape over the electrodes on forehead and the temples, e.g., F7, Fp1, T1, F8, Fp2 and T2. Now you are ready to wrap the head. Two 4-inch self-adhering conforming bandages are used. Tape the head wrap for security and then place a net over the head, which is very convenient, especially for children. Eight patients per week were monitored and evaluated for diagnosis of Epileptic seizures vs. non epileptic spells.
Note: Since Grass EC2 cream was discontinued, SAC2 from spes medica usa could be used. Also, Natus EC2+ and/or Tensive.
Results: This method is fast, easy and convenient with no Collodion odor, no skin breakdown and easy electrode removal with just water. The electrodes remain secure on patients with severe epileptic seizures and autistic children. Electrodes continue with low impedance and practically no repairs on patients monitored for 3 to 4 days. This procedure is also for patients who are allergic to Collodion.
Conclusion: Epileptologists are able to see the beginning, evolution and end of the seizure.

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Modelling spatio-temporal dynamics of interictal spikes

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Purpose: The localization of the epileptogenic network from the analysis of interictal activity is still an open issue for patients with pharmacoresistant epilepsy. Compared with seizure events, interictal activity is also observable with both invasive (stereoelectroencephalography, SEEG) and non-invasive (magnetoencephalography, MEG) techniques, but is usually much easier to record. In this study, we build a whole brain network model personalized with patient specific data to predict spatio-temporal dynamics of interictal spikes.
Method: First, we simulated interictal spikes for a single node of the network with Epileptor, a phenomenological neuronal model of epileptic activity. For a single Epileptor model, the generation of spikes depends on the level of noise of the stochastic integrator used to compute the dynamics of the model. Then, we built and simulated a high spatial resolution neural field model composed of 20484 cortical (and 18 subcortical) nodes. This model embeds long-range and short-range structural connectivity, and accounts for complex spatio-temporal dynamics observed in epilepsy. Finally, we mapped the simulated brain activity to both SEEG and MEG measurements.
Results: For whole brain network modelling, short-range coupling is essential to recruit a sufficient number of nodes and to trigger the emergence of a significant interictal activity which then propagates through the network. Importantly, this activity is also observable in simultaneous SEEG and MEG synthetic data, with specific spatio-temporal patterns. We built personalized whole brain network for 10 patients and showed that the simulated SEEG and MEG signals had similar spatio-temporal patterns as empirical SEEG and MEG observations.
Conclusion: This work demonstrates the modelling of spatio-temporal dynamics of interictal spikes for individualized patients. It brings opportunities to better understand the relationships between interictal and ictal discharges using invasive but also non-invasive measurements. Finally, the multimodal dataset of this study is made available to the community.

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High-frequency oscillations in the high-density scalp eeg: identification of the epileptogenic zone

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Purpose: The use of non-invasive high frequency oscillations (HFOs) to accurately locate epileptogenic or seizure onset zone is promising. In this study, we explored the accuracy of HFO in localization of epileptogenic zone using non-invasive high-density scalp electroencephalo-

gram (EEG).
Method: We enrolled patients who underwent preoperative evaluation of epilepsy surgery at the Epilepsy Center of Beijing Tiantan Hospital, Capital Medical University from 2020 to 2022. One hour of 256-channel high-density EEG during the interictal period was recorded. Routine preoperative assessment was performed, and suspected epileptogenic zone were defined based on long-term video EEG monitoring, head MRI, PET/CT, and magnetoencephalogram results. The five-minute interictal EEG data (sampling rate 1000 Hz) was randomly selected, and ripples (80-200 Hz) were detected by our self-developed HFO automatic detection. The channels with ripples were selected as the regions of interest (ROIs) and compared with the epileptogenic zone.
Results: In the 29 patients, 19 (65.6%) had ROI based on the number of scalp HFOs that was consistent with the epileptogenic zone identified by conventional preoperative evaluation. Among them, 10 patients (52.6%) had ROI in the same brain region as the epileptogenic zone, and 6 patients (20.7%) had ROI partially overlapping with the epileptogenic zone.
Conclusion: This study proves that scalp high-density EEG can record interictal HFOs, and the recorded HFOs have clinical application value in the localization of epileptogenic zone and brain region.

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Asymmetric sleep in patients with focal epilepsy

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Purpose: Sleep engages delimited brain regions and sleep biomarkers have been shown to be modulated by cognitive and motor paradigms. Whether pathological activity can also impact the focal expression of sleep markers remains vastly unknown. Here, we investigated whether epilepsy can be associated with a perturbed expression of sleep-related activities.
Method: We retrospectivity included sixty-nine patients (29 females) with a lateralized epileptic focus (34 left-sided). We compared, between patients with left vs right focal epilepsy, the inter-hemispheric asymmetry of sleep slow oscillations power (0.5-4 Hz); spindles density (occurrence per min), amplitude, duration and locking to slow oscillations (estimated through the intertrial coherence); and sleep slow waves density, amplitude, duration and slope. We used a Fine Tree classifier to test if these population-based asymmetries reflect individual differences.
Results: We found significantly different asymmetries in slow oscillation power ($p<0.01$); slow wave amplitude ($p<0.05$) and slope ($p<0.01$); and spindle density ($p<0.0001$) and amplitude ($p<0.05$). Crucially, these asymmetries classified patients with an above-chance level of 65% (SD=5%). As expected, the asymmetry of interictal epileptiform discharges (IEDs) was even

better in classifying patients (75 ± 3%). Furthermore, it was slightly but significantly improved when the asymmetry of sleep markers was added to the Tree classifier (77 ± 4%).
Conclusion: Our work establishes that several markers of sleep are asymmetrically expressed in patients with focal epilepsy, including at an individual level. It also suggests that sleep markers carry additional information to IEDs, given the improved performance of the classifier when they are added to IEDs.

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Seizure clusters in ultra long-term subcutaneous electroencephalography

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Purpose: Seizure clusters (SCs) represent a series of seizures grouped consecutively with a short inter-seizure interval (ISI). SCs have been reported to directly affect the quality of life and increase morbidity and mortality risks in people with epilepsy (PWE). Current SC detection and corresponding treatment are based on data from the patient's seizure diary. However, seizure diaries have been shown to be <50% accurate. This analysis aims to explore the potential of ultra long-term subcutaneous electroencephalography (sqEEG) monitoring using a two-channel subcutaneous EEG monitor (24/7 EEG™ SubQ, UNEEG medical, Alleroed, Denmark) in terms of clustered seizures and compare the results with seizure diary.
Method: sqEEG data from 3 adults PWE with a total recording time of A. 230 days, B. 66 days, and C. 47 days were recorded and annotated for seizure events. SCs were identified from both electrographic seizure events and reported diaries based on the clinical definition of at least three seizures within 24h or two seizures with a maximum ISI of 6 hours (Bauman K. et al. *Front. Neurol* 2021; *12*, 159.)
Results: Reviewing sqEEG data found the number of electrographic seizure events / diary-reported events to be 31/21, 24/46, and 14/0 for patients A, B, and C, respectively. Moreover, comparing the SCs of the seizure diary / electrographic seizures revealed 6/10, 14/9, and 0/3 for patients A, B, and C, respectively.
Conclusion: A reliable seizure report is a prerequisite to proper SC detection. Our results show that just like the seizure count based on a diary is unreliable, so is the number of SCs. Over and under-counted diary-based SCs could lead to suboptimal treatment and increase the associated morbidity and mortality risk. We believe that reliable identification of SCs can potentially improve epilepsy management and hopefully increase the quality of life for PWE.

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Modelling re-entry excitation and interventions in a personalized cortical model of epilepsy

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Purpose: Current treatment options for epilepsy are medication, surgical removal of the epi-

leptic tissue and stimulation. Success rates of surgical and stimulative interventions are in the range of 50% to 70%, leaving room for improvement. Computational modelling and dynamical systems theory can help to further our understanding about seizure dynamics and provide us with the possibility to test intervention strategies in-silico.
Method: We built a high resolution personalized computational model of a patient with drug resistant focal epilepsy in the left temporal lobe. T1 weighted and diffusion MRI together with tractography were used to reconstruct the cortical surface and to estimate connections between points of the surface on the scale of $1mm^3$. A two dimensional dynamical model, called the Epileptor, was used in an excitable regime to model seizure dynamics.
Results: We first simulated reentry excitation in a toy model of two delay-coupled 2D Epileptors. Then we equipped the cortical surface with the dynamical model and explored the parameter space of local and global coupling strength. We observed self-limiting excitations, spiral waves and sustained reentry excitation. We tested two intervention strategies trying to prevent reentry. Virtual surgery was applied to the white matter by lesioning fibre tracks and removing their contribution from the connectivity of the cortex. We also demonstrated phase dependent stimulation effects through virtually implanted electrodes.
Conclusion: We demonstrated that a high resolution personalized computational model can be used to simulate epileptic dynamics and test intervention strategies on a level of resolution that is necessary for real world applications. Future studies should focus on fine tuning the parameters of the model to fit it to the individual observed empirical data and optimize the intervention.

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Patterns of EEG abnormalities in patients with metabolic encephalopathy via single emergent EEG and emergent continuous EEG: a prospective study

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Purpose: To analyze various EEG patterns in patients of metabolic encephalopathy(ME)via both single emergent EEG and emergent continuous EEG.
Method: We prospectively recruited 100 consecutive patients with ME with altered sensorium admitted in critical care unit and performed bedside EEG continuously for 12 hours. The EEG patterns in the initial 30 minutes and at the end of 12 hours were analyzed.
Results: Out of 100 patients with ME, the EEG patterns observed were diffuse generalised slowing seen exclusively in 67% patients, Triphasic waves (TW) (21%), sleep spindles (4%), diffuse beta like pattern (4%), intermittent suppression (3%) and Frontal intermittent rhythmic discharges of adult(FIRDA) (1%) of patients. Seizures were noted in 18% of patients at presentation. Patients with low Glasgow coma scale (GCS) during admission and patients who had non-reactive EEG were associated with poor outcome. There was no statistically significant correlation with background of EEG and outcome of the patients (P value= 0.391). None of the patient had Non convulsive status epilepticus (NCSE).
Conclusion: The most common type of EEG abnormality in ME was diffuse bihemispheric

slowing seen exclusively in 67% of cases, while TW were observed in 21% of cases. The reactivity of EEG was significantly associated with better outcome. There was no difference in the yield of EEG at end of 12 hours of monitoring as compared to routine 30 minutes EEG

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Functional and structural analysis of patients with lateralized periodic discharges

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Purpose: Lateralized periodic discharges (LPDs) are a common EEG pattern in critically ill patients. They are considered in interictal-ictal continuum and may appear in a wide range of pathological conditions. The mechanisms behind the appearance of this pattern are not completely understood. In this study neuroimaging and clinical neurophysiology were combined to investigate LPDs features.
Method: 11 patients were investigated. All subjects were submitted to high resolution CT (5 patients) or MRI (6 patients) and EEG. Gray matter of the volumetric brain scans was automatically segmented and normalized into a standard space using SPM12 routines. All patients had LPDs visually identified in the EEG. For each patient, periodic discharges were automatically selected and averaged using BESA software. A tridimensional image of the source map using deterministic algorithm was obtained in the same space of the brain images. Finally, using Matlab, statistical analysis was conducted searching for correlation between the two methods (structural neuroimaging and EEG source maps).
Results: Mean age of the patients was 58±17 (34-78, 5 women). Mean number of periodic discharges analyzed was 173±262 (22-692). The etiology of LPDs was encephalopathy (n=5), status epilepticus (n=4), encephalitis (n=1) and structural (n=1). Statistical analysis showed areas of positive correlation between neuroimaging and LPDs mainly in the posterior quadrants involving left inferior occipital gyrus ($p<0.001$, 2390mm3) and the right middle temporal gyrus ($p<0.001$, 1919mm3).
Conclusion: It was demonstrated that cortical areas were positively associated with the LPDs discharges despite of the multiple etiology. This heterogeneity of causes raises the possibility of a common mechanism underlying these phenomena. The positive correlation observed indicates that larger cortical volumes were correlated with increased current density in the EEG. Preservation of some cortical areas, as demonstrated here, may be necessary to LPDs.

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Intracerebral high-frequency oscillations and Mozart's music

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University Hospital, Brno, Czech Republic, [4]Faculty of Electrical Engineering and Communication, University of Technology, Department of Telecommunications, Brno, Czech Republic, [5]Institute of Computer Science, Masaryk University, Brno, Czech Republic

Purpose: We aimed to confirm the Mozart effect in epileptic patients using intracerebral electroencephalography recordings and the hypothesis that the listening Mozart´s music with similar acoustic properties leads to the influence of high frequency oscillations (HFOs) characteristics differentially in epileptic and non-epileptic hippocampus.
Method: Twenty-three epilepsy surgery candidates were implanted with depth electrodes also to the studied temporal medial area, either only within epileptogenic hippocampus (5 patients) or non-epileptogenic hippocampus (10 patients), or in both hippocampi (7 patients). Patients listened to the first movement of Mozart's Sonata for Two Pianos K.448 or first movement of Mozart's Piano concerto K.595. Musical features of these compositions with respect to rhythm, melody, and harmony were similar. Subsequently, we studied the effect of listening to music on the occurrence and characteristics of HFOs within both types of hippocampi and compared the results statistically.
Results: In intracerebral electroencephalography the normalized HFO rates were significantly reduced by Mozart music in the range of ripples and fast ripples in the hippocampus independently of the presence of the epileptogenic zone. Interestingly, while reduction of ripples was more pronounced in pathological hippocampus, fast ripples were reduced in non-pathological. Even more interesting results were in relation to normalized relative entropy, in which a significant decrease occurred in the ripple band within the epileptogenic hippocampus only, compared to that in the fast ripple band just within the non-epileptogenic hippocampus.
Conclusion: We confirmed the decrease in the occurrence of HFO while listening to classical music. While music influenced the occurrence and characteristics of fast ripples mainly in the non-epileptogenic hippocampus, the opposite was true in the ripple range. Using music, it would theoretically be possible to distinguish between epileptogenic and non-epileptogenic areas, and thus determine the lateralization of the epileptogenic hippocampus.

Supported by project nr. LX22NPO5107 (MEYS): Funded by European Union – Next Generation EU.

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Effects of Brivaracetam add-on therapy on EEG power spectrum and connectivity

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Purpose: Brivaracetam (BRV) is a recent antiseizure medication approved as an add-on therapy for people with focal epilepsy. BRV has a good efficacy and safety profile. However, its specific effects on resting state EEG activity are unknown. The aim of this study was to evaluate the EEG power spectrum and connectivity changes induced by BRV add-on therapy in a sample of adult patients with focal drug-resistant epilepsy (DRE) compared to healthy subjects (HS).
Method: We performed a longitudinal, retrospective, quantitative EEG study on 23 patients with DRE and 25 HS. Clinical outcome was dichotomized into "good outcome" (>50% reduction in seizure frequency) and "poor outcome" (no modification or <50% reduction in seizure frequency) after one year of add-on therapy with BRV. EEG parameters were compared between HS and patients with DRE at baseline (EEGpre) and after 3 months of BRV (EEGpost). We investigated BRV-related changes in EEG Power Spectrum Density (PSD) and global connectivity using Phase Locking Value (PLV).
Results: BRV therapy did not induce significant changes in all frequency band PSD values that resulted in significantly lower values in DRE patients compared to HS at both times (EEGpre; EEGpost; $p<.05$). In addition, considering all patients' sample, BRV did not affect EEG connectivity, showing significantly lower PLV values in all frequency bands at both times compared to HS ($p<.05$). Finally, only in patients with "good outcome" BRV induced an increase in theta band connectivity in EEGpost compared to EEGpre condition, resulting in a 'normalization' of PLV values with no differences compared to HS.
Conclusion: BRV induced a significant increase in theta band connectivity only in patients who achieved good seizure control after therapy without affecting the EEG power spectrum. Our findings could help us understand the effects of BRV on the central nervous system and predict drug responsiveness in DRE patients.

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A wearable EEG based driver drowsiness detection and alert system for accident prevention

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Purpose: Drowsiness is a transition state between wakefulness and sleep associated with decreased alertness. The aim is to develop prototype software for drowsiness detection by processing EEG signals using offline data.
Method: The EEG signals are gathered from the general-purpose open repository Zenodo operated by CERN. 10 data sets were used with sampling frequency of 512 samples per second. Each session consisting of ten blocks of ten seconds of EEG data recording with two conditions such as five blocks with eyes closed and others with eyes opened. Absolute and relative alpha powers were determined by using power spectrum density and fast Fourier transform

(FFT). The power spectral density and FFT were computed using the Welch method in python programming language. Only one EEG channel O1 was used and was divided into frequency bands of continuous 10 seconds of data segments. The absolute and relative power of alpha was computed.
Results: Statistical analysis was done by using SPSS version 21. T-test was performed between two conditions at $p<0.05$. The result shows that alpha band powers increases from eye opened state to eye closed state.
Conclusion: Utilizing the alpha power band spectrum and a single electrode in the occipital region, the transition from wakeful state to drowsiness can be detected. This would be the preliminary step in creating an algorithm based software and hardware which can be used as an alarm to awaken long distance drivers from the sleep related road traffic accidents.

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Slow-wave electrographic shifts in iEEG, LFP, and single unit data at the pre- and postictal transition

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Purpose: DC-shifts have been proposed as potential biomarkers of seizure onset zone localization and slow-wave components have been described as postictal phenomena, such as spreading depolarization. Combined depth-electrode and microwire recordings in epilepsy patients provide a clear means for testing the involvement of these slow-wave components in ictal events. Here we provide evidence of a DC-shift phenomenon detected at the pre- and postictal transition in epilepsy patients with implanted hybrid macro/micro depth electrodes.
Method: Data from 12 seizures (4 patients with medial temporal lobe epilepsy) were recorded using bilaterally implanted Behnke-Fried depth electrodes with 8 high-impedance platinum-iridium microwires protruding a few millimeters from their tips, allowing simultaneous recording of the local field potential (LFP) and unit data along with the intracranial EEG.
Results: We observed a DC-shift component recorded in hippocampal regions, the entorhinal cortex and the piriform cortex that was detected in 82% of the depth electrodes in which an ictal event was also noted. When observed at the ictal onset, the slow-wave component was present in the LFP traces from microwires. Similarly, 15% (10 out of 144 channel recordings) of the LFP traces showed a high-amplitude DC-shift at seizure termination. Analysis in the frequency domain suggests a postictal power increase in the 0-1 Hz range when compared to baseline.
Conclusion: Our results show that slow wave electrographic components can be observed in human epilepsy patients using depth-electrode recordings. Additionally, these DC shifts have the potential to shed light upon the mechanisms involved in seizure initiation and termination. Moreover, we propose that the presence of a slow-wave electrographic feature at the ictal onset could provide a technical advantage for the use of microwires in clinical determination of the seizure onset zone and could lead to a mechanistic understanding of the ictal

transition phase in human seizures.

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Home video telemetry (HVT) – is it the wave forward?

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Purpose: To examine the effectiveness of HVT in patients with frequenct paroxysmal events.
Method: Home Video Telemetry (HVT) is a relatively new clinical service within the Neurophysiology world. At present the Clinical Neurophysiology Department in St James's Hospital has a very successful ambulatory EEG service . Outpatient ambulatory EEG recordings have distinct advantages and disadvantages; the lack of video to accompany the EEG data can at times greatly hamper the interpretation of a patient's event and can delay a diagnosis. In addition, differentiating between artefacts and actual epileptiform patterns without video can be a challenge in itself.
Patients waiting for an ambulatory EEG were contacted by a physiologist and undertook a detailed questionnaire, if clinical history met the criteria; they were subsequently offered HVT for a 24 hour period using the Cadwell Apollo Arc system. We implemented the service and reviewed the outcomes both clinically and technically for this small cohort of patients.
Results: 10 patients were offered HVT, 8 patients accepted. Majority of patients were female , with a mean age of 24. In 7 patients an habitual attack was captured, answering the clinical question. In 4 cases the event were deemed to be epileptic in nature. All studeis were of a good quality from a technical perspective.
Conclusion: Although the number of patients investigated is not large; we have clearly demonstrated the utility of short HVT in selected patient's. We hope to expand this service in the near future.

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Delineating the dynamics of ictogenic and irritative zones using machine learning of interictal epileptiform discharges in paediatric stereo-electroencephalography

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Purpose: Interictal epileptiform discharges (IEDs) are theorised to be transient electrographic features of excessive inhibition within the hyperexcitable cortex (Michelson and Wong, 1994).

IEDs are seen within parts of the cortex which generate seizures (ictogenic cortex) and those which do not (irritative zone). The current literature states that a lack of IED variance indicates an ictogenic zone (Conrad *et al.*, 2020). In contrast, patients with excess spike variance have a worse post-surgical outcome (Klimes *et al.,* 2022). Furthermore, studies suggest that resectioning a larger proportion of the irritative zone can improve post-surgical outcomes. Still, in some patients, this needs to balance with safety and risk of cognitive deficit (Bautista *et al*.,1999). We wanted to answer the questions, one, can we define different groups of IEDs by their dynamics and two, do IED group dynamics differ between interictal and preictal states?
Method: In five patients with refractory epilepsy who underwent SEEG implantation, we clustered IEDs using a machine learning (ML) algorithm. For each cluster, we calculated inter-ictal and pre-ictal spike rates. Interictal data was collected 24 hours before the seizure and pre-ictal data one hour before the neurophysiological onset of the seizure. In addition, we calculated a z-scored spike rate. Pre-ictal spike rates were corrected using interictal Z-scores.
Results: We were able to cluster IEDs by spatial, temporal and morphological variance. The clustering of IEDs reveals significant dynamics. Cluster pre-ictal dynamics deviate from the interictal baseline and are heterogenous within the irritative cortex. In clusters within or near the ictogenic onset, the majority of clusters demonstrated a significantly increased IED rate in the hour preceding the seizure.
Conclusion: ML can be used to differentiate spikes and has the potential to delineate between irritable and ictogenic cortex. This information could be used to support surgical planning.

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Modulation of excitation/inhibition balance at epileptic focus in human: analyzes of induced activities by single-pulse electrical stimulation on the focus and seizure propagation zone

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Purpose: Cortical responses to single-pulse electrical stimulation (SPES) called early responses (cortico-cortical evoked potential: CCEP, 10-50 ms after SPES), delayed responses (DRs, 100-1000 ms after SPES), and their associate high-frequency activities (HFAs) have been investigated as possible surrogate markers of epileptogenicity. We succeeded in investigating the responses to SPES upon stimulus sites using a special switching device and compared cortical excitability between epileptic foci and other cortical areas.
Method: We recruited 5 patients with drug-resistant focal epilepsy who underwent intracranial EEG for presurgical evaluation (IRB#C1192/C1212). We applied SPES (0.2 or 0.5 Hz) at various intensities to 9 seizure-onset zones (SOZs) and 6 control cortices (CTL). Post-stimulus

HFAs at the stimulus sites by short-time Fourier Transform were compared between SOZ and CTL. In the systematic SPES at 1 Hz to all implanted electrodes, the occurrence rate of DRs in the SOZs was compared between stimuli on the SOZ itself and that on the seizure propagation zone (PZ).
Results: The stronger the stimulus intensity, the post-stimulus HFAs decreased in all electrodes except for 1 SOZ. The HFA significantly decreased more on SOZ than CTL. DRs were induced in 5 SOZs by SPESs on SOZs and PZs. The occurrence rate of DRs by stimulating SOZs (10.8±5.8%) was lower than that by stimulating PZs (19.6±5.7%). The DRs by SOZ stimuli tended to occur at the timing around the end of HFA decrease.
Conclusion: SPES at the site of stimuli induced HFA decrease especially on SOZ and DRs at SOZs were less induced by SPES on SOZ itself than on PZ. These findings may imply the vulnerable property of excitation/inhibition balance at epileptic focus.

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Headache and EEG: an interesting phenomenon

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Purpose: Brunei is located on the north-west coast of the island of Borneo in Southeast Asia with a population of 460 345. BNSRC is the tertiary Neurosciences centre which provides comprehensive neurological services in Brunei. The relationship between headache and EEG changes has not been fully elucidated. We aim to describe EEG abnormalities in patients whose main presenting complaint is headache.
Method: EEG requests with headache as the main presenting complaint were extracted from database of EEG requests from April to December 2020. Information on these patients and EEG reports were further reviewed from BRUHIMS (local EMR).
Results: There were 35 patients presenting with headache (15 (42.8%) male and 20 (57.2%) female, median age 39) identified to have undergone EEGs. In addition to headache as the main complaint, common additional symptoms included paraesthesia in head and limbs in 5 (%) patients, loss of consciousness in 4 patients, visual symptoms in 4 patients, confusion in 3 patients and focal weakness in 3 patients. 9 other patients had no additional symptoms. 27 patients (77.14%) had normal EEGs and 8 patients (22.8%) had abnormal discharges. 3 EEGs had multiple epileptogenic focuses, 3 had single epileptogenic focus and 2 had occipital sharps. All patients were started on anti-seizure medications, in addition to primary headache management. 4 patients had good response, 2 had minimal response, 1 had no significant response and 1 defaulted follow up.
Conclusion: The relationship between headache and electrographic encephalography is still unclear. Even though not every headache patient should undergo an EEG, our experience suggests that in certain patients this can be of additional value, as further management can be instituted. Further study into this is warranted.

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Describing sleep in people with epilepsy based on ultra long-term subcutaneous EEG

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Purpose: Even though sleep and epilepsy are closely coupled, sleep is often not an integral part of seizure management (Nobili et al., 2021). An obvious reason is that we still do not fully understand the coupling, but just as importantly the current clinical practice lacks reliable tools to monitor and easily visualize objective sleep measures. However, the combination of ultra long-term EEG recordings and advanced machine learning could change that. In this work, we investigate objective sleep parameters in a cohort of people with epilepsy (PWE) using ultra long-term EEG recordings.
Method: Nine subjects were monitored with a two-channel subcutaneous EEG solution (24/7 EEG™ SubQ, UNEEG medical, Denmark) for approximately three months (Weisdorf et al., 2019).
A deep learning algorithm was used to segment EEG data into sleep stages, which were used to compute descriptive sleep parameters (e.g., total nocturnal sleep time (TNST) and wake-after-sleep-onset (WASO)) for each 24h. If more than 2 hours of data were missing between 00:00 and 6:00 the night was discarded. Average sleep parameters were computed for each PWE.
Results: Between 27 and 82 nights were included for each PWE [median: 56.0; SD: 18].
The median average TNST was 6:40h [SD: 0:59h; range: 4:53h, 7:39h] and the median average WASO was 0:49h [SD: 0:46; range: 0:10h, 2:38h]. All PWE had midday naps [% of days with naps - median: 29%; range: 2%, 51%].
The average sleep onset was between 22:35 and 01:49 with standard deviations between 0:47h and 3:04h.
Conclusion: We found that sleep parameters displayed considerable variation across time and individuals, with some PWE having severely reduced nocturnal sleep amount and highly increased WASO. Given the close relationship between sleep and epilepsy, objective measurements derived from ultra long-term EEG like the ones presented here would be valuable in the clinic to improve epilepsy management.

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Comparing long and short-term assessment of heart rate variability in Dravet Syndrome and the effect of sleep

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Purpose: Heart rate variability (HRV) is a promising prognostic biomarker in Dravet Syndrome (DS), but different studies are not always comparable, limiting its clinical application. Actually, multiple HRV parameters, analyzed over different timescales and in different states are reported. The aim of this study was to assess which HRV parameter is more reproducible and linked to clinical severity, analysing differences between wake and sleep.
Method: 56 patients with DS with available 24h-ECG Holter-derived HRV were screened to evaluate if they had EEG-derived ECG traces available within 1 month before/after the Holter recording date. A 5-minute period in the awake and sleep state were analyzed and correlated with the 24h-HRV. Subsequently, relevant clinical features such as age, a recent history of status epilepticus (SE), and frequent generalized tonic-clonic seizures (GTCS) were correlated to HRV parameters with multiple linear regression models.
Results: 31 awake recordings and 22 sleep recordings were included. HF was the parameter with the highest correlation awake (Rho 0,745, p<0,001) and in sleep (Rho 0,727, p<0,001). Age was a significant factor in simple models for most parameters except RMSSD. A recent history of SE was associated with a significant reduction of HRV both in simple and multiple regressions for all parameters except for awake LF and for sleep RMSSD and PNN50. Frequent GTCS were associated with a significant decrease in sleep RMSSD, HF, and LF, also when correcting for the effect of age and history of SE. When compared pairwise, a significant increase in sleep was seen for HF (median +24,45 ms^2, IQR -7,51/+172,18 ms^2, p=0,036; increase in 15/22 patients).
Conclusion: A moderate degree of correlation between long- and short-term HRV was seen both in sleep and awake, and a strong correlation for awake HF. HF, both in wake and sleep, was significantly associated with high seizure burden, including SE and frequent GTCS.

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Interictal and ictal EEG source imaging in children below 6 years of age with curative epilepsy surgery: a retrospective, blinded clinical study

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Purpose: To assess whether interictal and ictal EEG source imaging (ESI) on low-density scalp EEG can localize the epileptogenic zone (EZ) in young children below 6-years of age who underwent curative epilepsy surgery.
Method: The study was performed in 13 consecutive patients (<6 years) with refractory epilepsy referred for presurgical work-up (Saint Luc Hospital, Belgium). EEG was recorded with 19 channels using the 10-20 setup and the epileptologist (RS) marked the seizure onset. The patient's MRI was used to build a headmodel containing 6 tissues. The interictal ESI analy-

sis was performed on all available long-term EEG recording. Four clusters with the highest number of spikes were automatically detected. Then, the averaged spikes of clusters were localized at three time-points (onset, half-rising and peak). The ictal analysis was performed between -2s and +5s from the seizure onset (n=93). For each seizure, ESI was obtained in every 2-second sliding window with 1-second overlap. In each time bin, time-frequency (TF) analysis followed by region growing was performed and two TF islands with the highest energy were chosen and localized. Finally, two expert electrophysiologists (RS and RET) interpreted all results and compared them to the resection zone (RZ) obtained from the post-operative MRI at a sublobar-level. According to the known surgical outcome after 1-year follow-up, the performance was measured by calculating the sensitivity, specificity and accuracy.
Results: Sensitivity, specificity and accuracy of interictal ESI were 60%, 66% and 62%, respectively. Ictal ESI showed a sensitivity of 80%, specificity of 33% and accuracy of 69%. When combining both methods in a parallel testing, , sensitivity and specificity were led to 48% and 77%.
Conclusion: Interictal and Ictal ESI seem to accurately localize the EZ in this very young group of patients. The combination of both can increase the diagnostic performance, especially in patients with non-lateralizing EEG abnormalities.

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Periodic Discharges (PDs) in patients with brain tumor pathology: clinical and electrophysiological features

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Purpose: Periodic discharges (PDs) represent an EEG pattern commonly found in association with focal cerebral lesions, particularly brain tumors (BT). The clinical interpretation of PDs is controversial as well as their pathophysiological origin. The aim of this study is to describe the prevalence and characteristics of PDs in patients with BT, focusing on their association with epilepsy diagnosis and status epilepticus (SE).
Method: Adult patients suffering from BT who underwent a video-EEG recording were retrospectively selected from the Neurology Clinic of "G. d'Annunzio" University of Chieti-Pescara from January 2016 to January 2023. Demographics, clinical features, as well as tumor characteristics, and radiological findings, were collected. Video-EEG data were reviewed to identify patients with PDs. Diagnosis of epilepsy and SE were made according to ILAE criteria.
Results: 175 patients (115 primitive BT, mean age 61.3; 60 metastatic BT, mean age 70.1) were enrolled. Thirteen patients (7.4%) showed PDs at video-EEG, of whom 12 with primitive BT. Patients with PDs presented lateralized PDs (LPDs) in most cases (84.6%), with a mean frequency of 1.25 Hz and temporal lobe localization in 76.9%, concordant with the tumor lesion side in 66.7% of the cases. Nine patients suffered from epilepsy, whereas SE was described only in three patients. Comparing primary BT with and without PDs, patients with PDs

presented more often a parieto-occipital lesion localization (p=0.01) and high-grade histology (p=0.01). No differences were observed according to sex, age, lesion dimension, and lateralization.
Conclusion: PDs can be more frequently observed in high-grade primary BT with parieto-occipital localization instead of metastatic BT. In addition, PDs are highly associated with epilepsy diagnosis but hardly ever can represent an ictal pattern.

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Blood-brain barrier-associated proteins are not elevated in serum of FIRES patients

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Purpose: A prominent clustering of Th1-associated cytokines found in febrile infection–related epilepsy syndrome (FIRES) patients suggests its central role of the pathogenesis. There is increasing evidence supporting the use of Tocilizumab, a humanized monoclonal antibody against the interleukin (IL)-6 receptor, to reduce the seizure burden in FIRES. However, Tocilizumab poorly cross the blood–brain barrier (BBB), suggesting its role in the pathogenesis of FIRES. Literatures focusing on the BBB in FIRES remain scarce. We aim to identify the role of BBB in FIRES through evaluation of BBB-associated cytokines.
Method: From 2011–2017, pediatric patients presenting as acute encephalitis without known pathogens were recruited for a longitudinal explorative study. We focused on patients diagnosed with FIRES and included patients with anti-N-methyl-D-aspartic acid-receptor (NMDAR) encephalitis and intractable epilepsy for disease controls. Serum cytokines in patients with FIRES and anti-NMDAR encephalitis were serially examined in acute and chronic phases for identification of cytokine evolution.
Results: There were 6 FIRES patients, 13 anti-NMDAR encephalitis patients and 11 patients with intractable epilepsy as disease controls. Although univariate analysis revealed that serum IL-2 and intercellular adhesion molecule 1 (ICAM-1) levels were highest in FIRES patient during active phase, none of the BBB-associated cytokines had significant alteration between active and chronic phases in FIRES patients. On the contrary, levels of BBB-associated cytokines including ICAM-1 and vascular cell adhesion molecule 1 (VCAM-1) in patients with anti-NMDAR encephalitis were significantly increased in chronic phase compared to that in active phase.
Conclusion: In our study, two of the BBB-associated proteins, ICAM-1 and VCAM-1, were lack of cytokine evolution during disease course in FIRES, whereas significant elevation were found in anti-NMDAR encephalitis patients. This finding suggested that ICAM-1 and VCAM-1 played a role to cause BBB dysfunction in anti-NMDAR encephalitis rather than FIRES patients. Other pathway causing BBB disruption in FIRES requires more investigation.

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A case of subacute encephalopathy with seizures in alcoholics (SESA) presenting with non-convulsive status epilepticus

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Purpose: SESA syndrome is a rare but distinct clinical entity which is an important consideration in patients presenting with an encephalopathy against a background of alcohol excess. This case outlines the presentation, diagnostic approach, and management of one such case in a large tertiary hospital.
Method: A 76-year-old right-handed male who was admitted with a low GCS , dense left hemiparesis and haemodynamic instability against a background history of chronic alcohol excess. He was transferred to the intensive care unit following intubation and ventilation in the emergency department. He had a CT head non-contrast which did not reveal an acute intracranial abnormality.
Results: EEG demonstrated near continuous high amplitude lateralised periodic discharges (LPDs) at 1-2Hz over the right hemisphere which evolved into continuous electrographic seizures consistent with a right hemispheric non-convulsive status epilepticus. He received a loading dose of levetiracetam. An MRI brain was demonstrative of multiple cortical and subcortical T2 hyperintensities with associated diffusion restriction throughout the right cerebral cortex as well as similar changes identified within the right thalamus and the left cerebellar hemisphere. These findings were felt to be consistent with seizure-related change. Clinical and electroencephalographic stabilisation was achieved with levetiracetam, lacosamide, and lorazepam. His EEG post treatment remained attenuated over the right hemisphere and he had a persistent left hemisparesis.
Conclusion: SESA is a rare and typically under-recognised syndrome which can present as a new neurological disorder in patients with a history of alcohol excess. It is important to consider this diagnosis in patients with a background of alcohol excess who present with typical clinical, electroencephalographic, and neuroimaging features as it requires a particular diagnostic and management approach. These patients require long-term treatment with antiseizure medication to reduce the risk of recurrence.

Comorbidities

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Protective effects of melatonin in a rat model of post-stroke epilepsy

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Purpose: Apart from mortality, we should attend to the disabilities of stroke survivors. Post-stroke epilepsy (PSE) is defined as recurrent epileptic seizures following stroke. Many stroke models with low success rates have been used to study the mechanisms behind PSE. We aimed to develop a novel rat model of post-stroke epilepsy.
Method: Altogether 92 male Sprague-Dawley rats were used. In this PSE model, temporal lobe epilepsy (TLE) was induced one week after photothrombotic stroke. Rats in the control group had sham photothrombotic stroke with TLE induction. Video monitoring was used to detect the frequencies of spontaneous recurrent seizures (SRS) 6 to 8 weeks after induction of TLE. Morris water maze, open field, approach-response, touch-response and pick-up tests were used to analyse spatial memory, anxiety, and aggressivity. In addition, we evaluated the benefit of melatonin as a treatment in this PSE model, and rats of the control group received the vehicle. Rats were euthanized after the completion of all behavioural tests to obtain the brains for further study.
Results: Significant differences in impaired spatial memory ($p < 0.01$), reduced exploratory behaviour ($p < 0.001$), aggression intensity ($p < 0.001$) and brain atrophy ($p < 0.001$) were found between the PSE group and TLE only group. However, there was no significant difference in SRS frequency. Treatment with melatonin mitigated impaired spatial memory ($p < 0.05$) and reduced exploratory behaviour ($p < 0.05$), aggression intensity ($p < 0.001$) and brain atrophy ($p < 0.001$) when compared to the vehicle group. The treatment did not significantly reduce SRS frequency.
Conclusion: A rat PSE model combining TLE and photothrombosis is established. Spatial memory, exploratory behaviour, aggressivity and brain atrophy but not SRS frequency are worse for in the PSE group. Melatonin treatment has protective effects on spatial memory, exploratory behaviour, aggressivity and brain atrophy but does not affect the SRS frequency.

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Sex-related differences in children and adolescents with functional dissociative seizures in a Brazilian tertiary epilepsy center

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Purpose: We evaluated possible sex-related differences in the demographic, clinical factors, and semiological aspects of children and adolescents with functional dissociative seizures (FDS) in a tertiary epilepsy center.
Method: In this unicentric and retrospective study, we reviewed medical files of children and adolescents (7-17 years) with FDS. After homogeneity tests, we used t-test and chi-square to compare boys and girls regarding 1. demographic (age); 2. FDS-factors (age onset; diagnosis delay; epilepsy presence; family history of epilepsy; neurological diagnosis; numbers of seizures during monitoring; average seizure frequency); 3. predisposing factors (physical, sexual and psychological abuse; dysfunctional family; school issues; types of school issues; the

presence of possible stressors; types of possible stressors); and 4. semiology findings (aura; unresponsiveness; side to side head turning; closed eyes during the FS; minor motor or focal motor; generalized motor; ictal crying; urinary incontinence; ictal injury).
Results: Fifty-three consecutive patients (32 girls [60.4%], 21 boys [39.6%] with a median age of 13.0 years; a mean of 12.81 years [SD=3.15]) composed this sample. Age at diagnosis, age of FDS onset, number of seizures during monitoring, and ictal crying semiology differed between boys and girls. Boys with FDS showed earlier age at diagnosis (p=0.004), earlier age FS onset (p=0.036), more frequent events during monitoring (p=0.038), and more frequent ictal crying semiology (p=0.049).
Conclusion: In our series, there was a slight predominance of girls (F: M = 1.52:1). Sex differences were not found in predisposing variables. Our data showed differences considering the age at onset, age at diagnosis, frequency of events, and semiology. Future studies with a larger sample are necessary to confirm these findings.

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Mixed seizures in multiple sclerosis, including psychogenic non-epileptic status epilepticus

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Purpose: The frequency of seizures in MS is rare but greater than that of the general population. Both neuro-inflammatory and neurodegenerative processes in MS may play a role in the pathogenesis of seizures, however, it is a further leap of understanding to grasp the pathogenic mechanisms that may lead to psychogenic non-epileptic seizures (PNES) in MS. We analyze the intersection of the pro-epileptic processes in MS and epileptic phenomena including psychogenic non-epileptic seizures which also can present in status.
Method: A 37 year old female was diagnosed with relapsing-remitting multiple sclerosis (RRMS) based on the well-established criteria of clinical presentation, neuro-imaging and presence of oligoclonal bands. Review of her unique case is presented here to evaluate this question further.
Results: The patient became pregnant just as disease-modifying treatment (DMT) was initiated and quickly discontinued. Psychogenic Non-epileptic Seizures began to occur, with duration up to 45 minutes on several occasions but ceased following delivery of a healthy infant at 33 weeks gestational age. As the patient resumed taking high dose anti-anxiolytic agents, she sustained an epileptic generalized seizure but no further events occurred. Neuroimaging during the pregnancy was not pursued as the clinical features of MS did not change, however, MRI obtained following the drug-related seizure showed no change in MS lesion burden. Electroencephalogram was repeatedly confirmatory of the diagnosis of PNES during this period.
Conclusion: The pathophysiologic basis of PNES involves alterations in motor and emotion-processing networks within the brain but whether this is in cortical or deeper regions is unclear and understudied. MS-related pathology, directed to the temporal lobes especially, may possibly be involved with the provocation of seizures complicating MS. Indeed, similar

mechanisms that promote neuronal excitability and epileptogenesis may play a role in both types of seizures and this is an area that calls for further investigative study.

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miRNAs: serum-based biomarkers for the development of intellectual disability and autism spectrum disorder in tuberous sclerosis complex

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Purpose: Tuberous sclerosis complex (TSC) is a rare multi-system genetic disorder characterized by high incidence of epilepsy and neuropsychiatric manifestations known as tuberous-sclerosis-associated neuropsychiatric disorders (TANDs), including autism spectrum disorder (ASD) and intellectual disability (ID). MicroRNAs (miRNAs) are small regulatory non-coding RNAs that regulate the expression of more than 60% of all protein-coding genes in humans and have been reported to be dysregulated in several diseases including TSC. Recently, miRNA levels in serum have received increased attention as non-invasive biomarkers. Given the broad spectrum of TANDs at a behavioral, psychiatric, intellectual, neuropsychological level, identification of these biomarkers can aid in the early prediction of neuropsychiatric comorbidity development, resulting in early intervention.
Method: Thus, in the current study, RNA-sequencing analysis was performed to evaluate miRNA expression patterns in serum of infant TSC patients (aged 0-3 months). A Receiver Operat-

ing Characteristic (ROC) curve analysis was used to identify circulating molecular miRNA biomarkers able to discriminate the development of neuropsychiatric comorbidity, either ASD, ID or both, in infant patients with TSC. Verification of biomarker potential was performed using RT-qPCR for the identified miRNAs.
Results: This study identified multiple promising miRNA biomarkers for the early prediction of ASD, ID or both in young TSC patients and verified the possible use of RT-qPCR for miRNA expression levels from serum. Moreover, these results show that miRNA expression could potentially predict the development of ASD and ID in TSC patients before formal psychological evaluation can take place.
Conclusion: With this, our results support the notion that circulating miRNAs have the potential to aid standard clinical testing in the early risk assessment of ASD and ID development in TSC patients. With this, parents could learn to improve their children's behavioral and social skills and reduce the impact of these comorbidities on their quality of life.

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Does sodium valproate play a role in carotid plaque pathophysiology?

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Purpose: Sodium valproate (SV) exposure has been reported to be associated with a reduced risk of myocardial infarction and recurrent ischaemic stroke (in particular, large artery stroke). Anti-atherogenic effects of SV may include interference with metabolic and epigenetic pathways underlying the balance between plaque instability and healing. However, atherosclerosis according to SV exposure has never been evaluated in vivo. We present preliminary data of a study (VATHERCA study) aimed to evaluate carotid plaque features in epileptic patients taking (vs not taking) SV.
Method: In an observational, case-control, multicenter study, we considered epileptic patients aged $\geq$ 50 years undergoing duplex scan of carotid arteries. Two groups of epileptic patients (exposed to SV vs not exposed to SV) were compared, searching for potential differences in carotid plaque features (degree of stenosis, echogenicity according to Gray Weale/Geroulakis classification, surface). Intima-media thickness was evaluated, too.
Results: 29 patients (female 14/29, 48,3%; mean age: 63.4 years, range 50-80) were considered. 18/29 (62,1%) patients were on SV therapy, the remaining assuming other anti-seizure medications. Demographic, vascular risk factors and neurosonological features didn't differ between groups, including frequency of carotid plaques (3/18, 16,7% in SV group vs 3/11, 27,3% in the control group), causing stenosis $\leq$50% in all cases. Of note, all patients in SV group presented type 4 plaques (i.e. uniformly hyperechogenic), while plaques in the control group were more heterogenous.
Conclusion: Our research project is the first "in vivo" study aiming to explore neurosonological parameters in epileptic patients assuming SV; limited, preliminary data showed that all

patients exposed to SV presented a stabilized carotid plaque, suggesting potential protection of SV against plaque vulnerability. SV may contribute to stabilization of carotid artery plaque, but further research involving larger numbers of patients is needed to better elucidate such issue.

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A retrospective analysis of incidence, aetiology and progression of seizures in post-liver transplant patients

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Purpose: Seizures in the immediate and extended post-operative period of liver transplantation can cause significant mortality, morbidity, and prolonged hospital stay. There is limited data available regarding post-liver transplant seizures worldwide. This study aimed to elucidate the aetiology of post living donor liver transplantation (LDLT) seizures and compare their baseline parameters with the controls.
Method: Retrospective analysis of adult LDLT recipients at our center revealed 81 cases of post-operative neurologic complications, 42 of whom presented with seizures from 2009 to 2022. Compared to 2853 controls of the same population, their pre-operative parameters, comorbidities and aetiologic factors were analyzed from day 1 to day 180 of post-operative period along with magnetic resonance imaging (MRI) and electrophysiologic studies.
Results: The incidence of seizures was seen in 51.8% (n=42) patients with neurologic complications. Seizures were most commonly generalised in semiology (83.3%, n=35) and were more common in alcoholic patients (n= 23, p=0.88). More than one-third (40.6%) of the patients that could undergo MRI had a structural cause on imaging, including strokes and posterior reversible encephalopathy syndrome (PRES) (n=13, p=0.86). Electroencephalogram (EEG) study showed normal results or mild slowing in 73.3%, 16.5% showed severe slowing, two had focal discharges and one patient had non-convulsive status epilepticus (3.3%). After multivariate analysis, those with advanced age, higher MELD score, and pre-existing minimal hepatic encephalopathy fared worse.
Conclusion: Seizures can complicate a significant number of LDLT recipients' course of treatment. A structural pathology always needs to be ruled out at the onset. Modifiable risk factors such as pre-operative pneumonia, renal dysfunction, and deranged total leukocyte count can be corrected to reduce incidence of neurologic complications after liver transplantation. Keeping a watchful eye over those with advanced age, a higher MELD score and alcoholic liver disease can alert the transplant physician in time to diagnose and treat seizures in good time.

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Unravelling the non-pharmacological therapeutic needs associated with Dravet syndrome

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Purpose: Dravet syndrome (DS) is characterised by a drug-resistant epilepsy and severe comorbidities that are variable across subjects. This disease is usually associated with cognitive and behavioural disturbances, intellectual disability, motor and sleep disorders and autistic spectrum traits. In contrast to the large number of studies concerning pharmacological treatments, little has been described about non-pharmacological options for DS. This study aimed at investigating the non-pharmacological therapies received by DS patients and their economic impact on their caregivers and families.
Method: We developed an online survey aimed at families and caregivers of DS patients in order to examine the non-pharmacological therapeutic needs of DS patients and the socio-economic impact of those therapies on families. Specifically, we focused on: 1) demographic and clinical data; 2) non-pharmacological therapies; 3) educational needs.
Results: We recruited 62 participants (31% females), with a mean age of 12 years (range: 9 months-51 years). Our results indicated that up to 91.9% of the patients surveyed used non-pharmacological therapies, mainly aimed at treating cognitive, sensory and motor impairments. Our study shows that, in most of the cases, these therapies are beneficial for the patients. However, they also represent high financial costs which are usually borne entirely by the families.
Conclusion: The support required by DS patients concerns not only the pharmacological needs, but also all the needs related with the multiple comorbidities associated with this disease. Furthermore, these comorbidities have an enormous socio-economic impact on the life of patients and their caregivers. Thus, our study encourages both the inclusion of the costs associated with non-therapeutic interventions in the national health system and suggests a better coordination of a multidisciplinary team, including psychologists, occupational and speech therapists, and professionals able to support also the special educational needs of these patients.

We would like to thank Takeda for providing the funding to develop this project.

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Anti-epileptic effects of REM sleep in Alzheimer's Disease

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Purpose: While seizures are well-known late neurodegenerative sequelae in Alzheimer's Disease (AD), recent studies have shown that epileptiform activity during sleep can present early in AD, which is associated with faster cognitive decline. However, these studies have demonstrated inconsistent findings on the sleep stage with most or least epileptiform activity owing to variable methodology across different species. Therefore, we conducted a systematic review on human AD and amnestic mild cognitive impairment (aMCI) focusing on the role of rapid eye movement sleep (REM), which is classically an anti-epileptic state.
Method: We searched MEDLINE and Embase using the following MeSH terms: "Alzheimer's Disease" AND "Epilepsy" OR "Seizures'' AND "Sleep" OR "REM". We reviewed additional articles based on references within initially identified relevant articles. Data was then extracted to determine distribution of epileptiform activity in REM and non-REM stages N1, N2, N3. We averaged percentages across studies. If a study had AD and aMCI subgroups, we averaged percentages to represent that study.
Results: Of 14 identified primary and secondary articles, 4 had sufficient quantitative data from a total of 111 AD or aMCI patients on epileptiform activity per sleep state. REM was least likely to be associated with epileptiform activity, with only 14.4% (standard deviation, SD 11.6%) of epileptiform activity in sleep. REM was then followed by N1, SWS and N2, with respective sleep-epileptiform activity percentages of 15.5% (SD 6.7%), 36.1% (SD 17.8%), and 34.1% (SD 9.9%).
Conclusion: While our findings confirm that REM sleep remained the most anti-epileptic stage of sleep, this anti-epileptic advantage was diluted when compared to non-AD studies. The possibility that sleep-related epileptiform activity in early AD relates to selective REM disruption requires
further research. In the meantime, therapeutic interventions in early AD may focus on improving REM to enhance whatever persistent anti-epileptic effect that remains in REM.

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Quality of life and depression phenotypes in young adults with epilepsy

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Purpose: Data on psychosocial functioning specific to young adults with epilepsy (YAWE) are limited despite developmental sensitivity of this phase. In epidemiological data, 51% of YAWE indicated a behavioral health/psychological comorbidity (Wagner J et al Epi Beh 2016;65:7-

12) with implications for quality of life (QoL). Study purpose was to use aggregate data from the Managing Epilepsy Well Network Integrated Database (MEW-DB) to: (1) describe sociodemographic and clinical characteristics; (2) analyze sociodemographic and mood variables as predictors of QoL in YAWE aged 18-29. Hypotheses: 1) after controlling for sociodemographic variables, suicidal ideation would be associated with lower QoL; 2) cognitive symptoms would predict greater variance in QoL compared to the somatic symptoms of depression, providing support for a cognitive phenotype of depression (Rayner et al Epi Beh 2016;64:336-44).
Method: Queried MEW-DB for all subjects aged 18-29 with completed standardized psychosocial measures of QoL (QoLIE-10) and mood (PHQ-9). N=237 had sufficient data. PHQ-9 was divided into cognitive (COG) and somatic (SOM) symptoms. Stepwise regression analyses (demographic variables, then separately: PHQ-9 suicidality item; PHQ-9 COG; PHQ-9 SOM; and PHQ-9 total score) were conducted.
Results: Respondents were =23.6 years old; 67.1% female, and 79.3% Caucasian. Most (77.2%) were not yet married or cohabitating; 67.4% reported some college education; 64.8% reported annual income < $25,000 USD/year. Epilepsy onset was =14.8 years; duration was =10.5 years. PHQ-9 total =10.0, (moderate depression). Suicide ideation (β=0.46 (95% CI=0.22, 0.71); p<0.001), COG symptoms (β=0.15 (95% CI=0.10, 0.19); p<0.001), SOM symptoms (β=0.15 (95% CI=0.11, 0.20); p<0.001), and total depression (β=0.09 (95% CI=0.07, 0.11); p<0.001) exerted independent effects on QoL.
Conclusion: This unique study leveraged aggregated data from a national database. YAWE have not been well-studied as a stand-alone group. Understanding correlates and predictors of depression has implications for YAWE as depression influences self-management program participation. Mood and QoL improve with self-management treatment.

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Collaborative care in post-traumatic epilepsy (CoCarePTE): design of a randomized hybrid effectiveness-implementation trial for anxiety and depression

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Purpose: Anxiety and depression in epilepsy are common and associated with poor outcomes, yet often untreated due to poor mental health specialist access. Collaborative care is an integrated care model with strong evidence base in primary care and medical settings, but

it has not been evaluated in neurology clinics. Further, it is important to evaluate implementation outcomes when translating evidence-based interventions to new clinical settings, to inform future scaling and incorporation into real-world practice.
Method: The Collaborative Care for Post-traumatic Epilepsy (CoCarePTE) study is a 2-site, randomized, single blind, hybrid type 1 effectiveness-implementation trial that will randomize 60 adults to neurology-based collaborative care versus usual care (NCT05353452). Adults with high anxiety or depression symptoms and history of at least mild traumatic brain injury prior to epilepsy onset will be enrolled. The collaborative care intervention is a 24-week stepped-care model with every 2-week care manager calls for measurement-based anxiety/depression care, seizure care monitoring, and brief therapy intervention delivery. This is supplemented by psychiatrist recommendations for neurologist antidepressant prescribing via case conferences and care manager-facilitated team communication. In step 2 of the intervention, individuals without symptom improvement by 10 weeks will receive an added 8 session remote cognitive behavioral therapy program. The study is powered to detect a moderate improvement in emotional quality of life.
Results: As a hybrid type 1 trial, effectiveness is the primary focus, with primary outcome being change in emotional quality of life in the intervention group vs. control. Secondary effectiveness outcomes are 6-month changes in depression and anxiety. Implementation outcomes are evaluated pre-implementation and at 3 months, including fidelity, acceptability, feasibility and appropriateness.
Conclusion: This trial is novel in its use of a hybrid effectiveness-implementation design to evaluate an evidence-based mental health intervention in epilepsy, and by incorporating seizure care into a collaborative care model.
Funding: Department of Defense, W81XWH2210630

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Development of international standard sets of outcome measures for infants, children, adolescents and adults with epilepsy in clinical practice: the international consortium for health outcomes measurement consensus recommendations

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Purpose: There is increasing recognition of the importance of delivering value-based health care, where value is assessed by measuring health outcomes against the cost of delivery. This approach leads to improved health outcomes for people with long-term medical conditions, with reduced healthcare utilisation by using well defined clinical and patient-reported outcome measures (PROMS). At present, there is no internationally agreed set of core outcomes for epilepsy clinical practice.
Method: The International Consortium for Health Outcomes Measurement convened an international working group of experts in epilepsy, people with epilepsy and their representatives. The group developed minimum sets of standardised outcomes and outcome measurement methods for clinical practice to support clinical decision making and quality improvement. The focus was to ensure international applicability, with a preference for measurement tools that have been validated in many settings, cultures, and languages and available at no cost.Measurement tool packages that capture all core outcomes were identified through Delphi based online consensus methods, with consecutive rounds of online voting supplemented by open discussion forums and external validation surveys over a 12-month period.
Results: 22 core outcomes were identified, of which many non-seizure outcomes were included: anxiety, depression, suicidality, memory and attention, sleep quality, somnolence, and neurodevelopmental status. Measurement tools including PROMS were recommended based on their evidence of strong clinical measurement properties, feasibility of implementation, acceptability to people with epilepsy and cross-cultural applicability. Different age-appropriate outcome measurement instruments have been recommended for use with infants, children, adolescents and adults with epilepsy. Additionally, case-mix factors and predefined time points for outcome measurement were suggested.
Conclusion: Implementing the proposed set of outcomes and measurement methods in daily practice should establish the use of patient-centred outcomes and ensure holistic care. Widespread adoption of consistent outcome measurement can reduce outcome measurement heterogeneity, facilitate big-data science, accelerate comparative research and lead to improved care.

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Overweight and obesity in patients with epilepsy

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Purpose: Overweight and obesity are a major civilization problem, which is relatively little known in the population of patients with epilepsy (PWE). Our purpose was to determine the risk factors of these conditions and to compare PWE with general population.
Method: The study included 401 consecutive PWE treated in the outpatient clinic over the years 2020-2021. Their weight and height were measured, BMI was calculated, and information was collected on demographic data, type and treatment of epilepsy, remission, degree of disability. An age and sex- matched control group was selected for comparison.
Results: A total of 401 patients (247; 61.6% women), median age 33.0 years, were included. The majority were patients with focal epilepsy (292 patients, 72.8%). BMI > 25 was found in a half of the cohort (197, 49.1%). The overweight and obese patients were older (38.0 vs 29.0 years, p< 0.001), had later epilepsy onset (17.0 vs 15.0, p = 0.016) and longer epilepsy duration (17.0 vs 14.0, p = 0.011). In this group, there were more patients with focal epilepsy (156, 79.2% vs 136, 66.7%, p = 0.005) and a disability certificate (100, 50.8% vs 76, 37.3%, p = 0.007. There were fewer people with higher education (41, 21.9% vs 76, 38.8%, p< 0.001) and currently employed (73, 37.2% vs 109, 53.7%, p = 0.001). There were no significant differences in the currently used antiseizure medications. In a multivariate logistic regression model, age (OR 1.06 [1.03-1.09], p<0.001) and male sex (OR 1,85 [1,15-2,97], p = 0.011) were identified as independent risk factors for overweight/obesity in PWE. In the control group, BMI>25 occurred statistically less frequently than in PWE (195, 38.2% vs 197, 49.1%, p<0.001).
Conclusion: Overweight/obesity appear to be more common in PWE than in general population, with older age and male sex being independent risk factors.

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AntiCD-20 treatment improves seizure frequency and severity in a patient with epilepsy and multiple sclerosis

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Purpose: To highlight the link between antiCD-20 imuunomodulatory treatment and seizure recurrence in a patient with multiple sclerosis and epilepsy.
Method: We present a 28-year-old female with focal epilepsy since the age of 13 years and multiple sclerosis diagnosed at 24 years who. After starting Ocrelizumab, she had a reduction in seizure frequency and required lower doses of antiepileptic drugs (AEDs).

Results: Initial seizure frequency was 1-3 focal seizures/month, including generalized tonic clonic seizures with trauma. She had multiple side-effects from AEDs, but managed to reach 4 seizures/year under two AEDs. After two episodes of transitory neurological deficits (diplopia and dizziness, language impairment for 1 week each, with spontaneous remission) in 2019 and 2020, she underwent a cerebral and cervical MRI in April 2020, and was diagnosed with multiple sclerosis, with multiple white matter and subcortical active lesions. She was started on Ocrelizumab in May 2021 and, using the same AEDs, experienced a reduction in seizure frequency and severity, then stopped one AED. The laboratory findings indicate a steady decrease in lymphocyte counts and complete depletion of CD19+ and CD20+ in 18 months after starting Ocrelizumab. The repeated EEG examinations indicate a marked decrease in interictal epileptiform activity. Repeated cerebral MRI examinations found no new active lesions, but a progression in the total number of lesions.
Conclusion: Anti-CD 20 treatment seems to have an influence on seizure frequency and severity in patients with epilepsy and multiple sclerosis, suggesting a link between increased neuroinflammation and the occurrence of seizures.

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Gastrointestinal and eating problems in *SCN1A*-related seizure disorders

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Purpose: *SCN1A*-related Dravet syndrome is a severe fever-sensitive epileptic encephalopathy, characterized by refractory epilepsy, intellectual disability, behavior problems, and additional comorbidities with a high impact on daily life. This study aimed to assess the prevalence and characteristics of gastrointestinal and eating problems in Dravet syndrome and other *SCN1A*-related seizure disorders and associations with other comorbidities.
Method: A cohort of 169 patients with an *SCN1A*-related seizure disorder, consisting of 118 (69.8%) patients with Dravet syndrome (DS) and 51 (30.2%) with GEFS+/FS (non-DS) , was evaluated. Gastrointestinal and eating problems were identified using a questionnaire developed by the researchers in consultation with a dietitian and a speech therapist. Associations between gastrointestinal and eating problems and syndrome specific comorbidities were tested with an ordinal logistic regression.
Results: Gastrointestinal and eating problems are highly prevalent in patients with Dravet syndrome. A total of 61.9% of patients with DS reported at least three symptoms associated

with a gastrointestinal or eating problem; in non-DS patients, this was 5.9%. The most prevalent symptoms were obstipation, choking on food, drooling, distraction during meals, and loss of appetite. Of patients with DS, 17.8% had a feeding tube, either for full intake or partly. In 51.7% of patients who experienced eating problems, parents reported a high impact on daily life. DS patients with motor disabilities (odds ratio (OR) 6.4 95%CI [2.3-17.5] p<0.05), who used more ASM (OR 5.0 95%CI [1.58 -15.7] p<0.05) and had severe behavioral problems (OR 2.8 95%CI [1.0 – 7.7] p=0.05) had more gastrointestinal or eating problems.
Conclusion: Gastrointestinal or eating problems occur frequently and are burdensome comorbidities in Dravet syndrome and should therefore be given appropriate attention by treating physicians. Early detection will enable a timely referral to a dietitian or speech therapist.

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Post stroke seizures in Brunei neuroscience stroke and rehabilitation center (BNSRC)

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Purpose: Stroke is the most common cause of epilepsy in the adult population. Post-stroke seizures (PSSs) are classified into early-onset seizures (ES) and late-onset (LS). In this audit, we identified stroke patients (n=222) with seizures admitted in Brunei Neuroscience Stroke and Rehabilitation Center (BNSRC) from April to September 2020. This is the first-time post-stroke seizure is described in the Brunei population. This study aims to estimate the frequency of seizures in patients with stroke in BNSRC, describe their demographics, stroke subtypes, seizure types and onset, and their electroencephalogram (EEG) findings.
Method: This audit retrospective reviewed the medical system, BRUHIMS and EEG laboratory database for patients with stroke and seizures.
Results: Seizure was noted in 18.5% (n= 41) of stroke patients admitted within the study period. The median age was 44 (37-90) years old; majority were males (66%). Most of the patients had ischemic strokes (n=31; 75.6%). Seizures occurred within 24 hours of stroke onset in 36.6% (n=15), within 1-7 days in 24.4% (n=10), and more than 7 days in 39.0% (n=10) of stroke patients. Most patients had focal seizures (n=26; 63.4%), followed by generalized (n=14; 34.1%), and focal onset to bilateral tonic-clonic seizures (n=1, 2.4%). Majority of the EEGs were abnormal (n=38; 92.68%). EEG findings included focal slowing (n=14, 34.1%), diffuse slowing (n=8, 19.5%), focal epileptiform discharges (n=10; 24.4%), focal onset to bilateral tonic-clonic discharges (n=6; 14.6%), multifocal discharges (n=2, 4.9%), and periodic lateralized and generalized discharges (n=2; 4.9%).
Conclusion: This study demonstrated that seizures are common in stroke patients in Brunei Darussalam. Majority of the seizures occurred within the first week of stroke onset, inverse to the global seizure onset trend. Focal seizures were the most common semiology and most patients had abnormal EEGs. Further study is recommended to determine the incidence of post—stroke epilepsy and its real-life impact in Brunei Darussalam.

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Psychiatric comorbidity in relation to clinical characteristics of epilepsy

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Purpose: Population-based surveys have shown a high prevalence of psychiatric disorders in people with epilepsy; but registry studies are often hampered by insufficient validity of the epilepsy diagnoses and scarce information about the nature of the seizure disorders. In a well validated and classified sample of patients with epilepsy, we investigate the associations according to clinical characteristics.
Method: Participants in The Trøndelag Health Study (HUNT 2 and 3, 1995-97 and 2006-08) with ≥ 2 diagnostic codes for epilepsy during 1987-2019 were identified. Medical records were reviewed, and epilepsy was validated and classified according to ILAE recommendations. Psychiatric comorbidity was defined by diagnostic codes from psychiatric departments during 1987-2022.
Results: A total of 448 patients with epilepsy were included. At least one psychiatric disorder was recorded in 35%; 23% had anxiety, 16% mood disorders, 7% substance abuse, 7% personality disorders, and 3% psychosis. Women had significantly more psychiatric comorbidity than men (41% vs 29%, p = 0.007). Comorbidity prevalence was similar in focal and generalised epilepsy. In focal epilepsy with structural etiology, it was significantly less common (p = 0.007), whereas it was more common in subjects with unknown etiology (p = 0.024). Comorbidity occurred slightly more often in those seizure free > 5 years compared to those with active epilepsy. Of 75 patients with epilepsy resolved, comorbidity was recorded in 39%. The majority of these patients had childhood onset seizures.
Conclusion: We found that just over 1/3 of subjects with epilepsy have psychiatric comorbidity. Comorbidity prevalence in focal and generalised epilepsy did not differ. Surprisingly, we found a slightly higher prevalence of psychiatric disorders in patients with > 5 years of seizure freedom compared to those with active epilepsy, and an even higher prevalence in those with epilepsy resolved, a group which often have non-acquired genetic etiology possibly also carrying a susceptibility to psychiatric disease.

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Attention deficit hyperactivity disorder and seizure type

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Purpose: The purpose of our study was to determine the frequency of distinct seizure type in patients with diagnosed with epilepsy and ADD/ADHD.
Method: Patients diagnosed with epilepsy and ADD/ADHD (confirmed by psychiatrist) were included in the study population. Details regarding patient demographics, type of epilepsy, seizure semiology and antiseizure medications were analyzed. Data was analyzed using SPSS, variables compared using chi-square test while t-test was used for comparing mean values of the groups.
Results: There are 2791 patients in the epilepsy database, 48.8% are men and 51.2% women. Mean age 38.1±23.1 years. 1379 patients were diagnosed with focal epilepsy, 729 with generalized epilepsy, 25 with combined, while 376 were unknown. 223 patients in the registry were diagnosed with ADD/ADHD. There were lower rates of ADD/ADHD in focal compared to generalized epilepsy cohort (27.8% vs 39.4%), including focal motor (18.8%) and non-motor seizures (5.8%) ($p<0.05$). In the generalized epilepsy group, generalized tonic-clonic seizure was the most common seizure semiology. A high rate was found for generalized non-motor typical absence seizures (12.1%) and atypical absence seizures (2.6%) ($p<0.05$). Patients with generalized epilepsy had higher odds of ADD/ADHD diagnosis compared to patients with focal epilepsy (OR = 1.4, 95% CI= 1.1-1.9). Patients with generalized epilepsy having a diagnosis of ADD/ADHD had a younger age at seizure onset compared to the group without a diagnosis (12.39±11.5 vs 18.5±11.5)($p<0.05$). No correlation with ASM was noted.
Conclusion: In this study, patients with generalized epilepsy have a higher incidence of ADD/ADHD compared to focal epilepsy. Generalized typical/atypical absence seizures were more likely to be associated with ADD/ADHD. Our findings are in accordance with studies that have reported correlations between absence seizures and attention disorders. Further studies are required to better understand the pathophysiological correlations that might exist between generalized epilepsy, absence seizures and attention deficit disorders.

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The genetic link between systemic autoimmune disorders and temporal lobe epilepsy: a bioinformatics study

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Purpose: We aimed to explore the underlying pathomechanisms of the comorbidity between three common systemic autoimmune disorders (SADs) [i.e., insulin-dependent diabetes mellitus (IDDM), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA)] and temporal lobe epilepsy (TLE), using bioinformatics tools. We hypothesized that there are shared genetic variations among these four conditions.
Method: Different databases (DisGeNET, Harmonizome, and Enrichr) were searched to find

TLE-associated genes with variants; their single nucleotide polymorphisms (SNPs) were gathered from the literature. We also did a separate literature search using PubMed with the following keywords for original articles: "TLE" or "Temporal lobe epilepsy" AND "genetic variation", "single nucleotide polymorphism", "SNP" or "genetic polymorphism". In the next step, the SNPs associated with TLE were searched in the LitVar database to find the shared gene variations with RA, SLE, and IDDM.
Results: Ninety unique SNPs were identified to be associated with TLE. LitVar search identified two SNPs that were shared between TLE and all the three SADs (i.e., IDDM, SLE, and RA). The first SNP was *rs16944* on the Ineterleukin-1β (IL-1β) gene. The second genetic variation was *ε4* variation of apolipoprotein E (APOE) gene.
Conclusion: The shared genetic variations (i.e., *rs16944* on the IL-1β gene and *ε4* variation of APOE gene) may explain the underlying pathomechanisms of the comorbidity between three common SADs (i.e., IDDM, SLE, and RA) and TLE. Exploring such shared genetic variations may help find targeted therapies for patients with TLE, especially those with drug-resistant seizures who also have comorbid SADs.

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Adverse effect profiling of persons with epilepsy in a tertiary care centre using LAEP scale: correlation with co-morbid depression

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Purpose: Anti-seizure medications(ASMs) are associated with multiple adverse events(AEs) that have a significant detrimental impact on quality of life and treatment adherence in persons with epilepsy(PWE). It is also known that PWE are at a risk for depression which can be drug or disease related. The aim of this study was to identify and quantify the AEs of ASMs using Liverpool Adverse Events Profile (LAEP), and to determine the feasibility of LAEP for predicting depression in PWE.
Method: After ethical clearance, 309 PWE >18 years of age, on ASMs, attending epilepsy clinic in neurology outpatient department(OPD) of All India Institute of Medical Sciences, New Delhi, India, were recruited and evaluated using Liverpool Adverse Event Profiling(LAEP) and different tools for depression namely MINI, NDDI-E, HAM-D and PHQ-9. Receiver operating curves(ROC) analysis was carried out to validate cutoff of LAEP for assessing depression, and the correlation between LAEP scores and depression in PWE was also determined.
Results: The mean LAEP scores in PWE were 28.2±6.2. PWE on polytherapy had higher LAEP score as compared to monotherapy(29.03±6.3 vs. 26.7±5.9; p=0.0013). Phenytoin had the highest LEAP score (28.7±9.8), followed by carbamazepine(27.8±5.3), levetiracetam(26.7±5.8), and sodium valproate(25.8±5.3). The percentage of PWE detected positive for depression were 38.8, 39.8, 43 and 43.4 with MINI, NDDI-E, HAM-D and PHQ-9 respectively. A

strong positive correlation of LAEP score was observed with depression assessed with different assessment tools. For screening of depression using LAEP as a screening tool, a cut-off of ≥ 28 is recommended as at this cut-off, sensitivity, specificity and the AUC curve of LAEP using MINI as reference standard were in acceptable range.
Conclusion: The systematic use of LAEP in epilepsy outpatient settings will allow for better detection and management of ASM's adverse effects, as well as the identification of PWE at risk of depression.

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Detection of cognitive impairment in patients with epilepsy through MoCA test and correlation with years with epilepsy in a sample of Mexican patients

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Purpose: To identify patients with cognitive impairment seen for the first time in an epilepsy clinic and to correlate the presence of cognitive impairment with sociodemographic variables and characteristics of the disease, such as type of epilepsy, time of evolution, and seizure control.
Method: Patients seen for the first time in the epilepsy clinic were evaluated. After obtaining the clinical history and physical examination, the MoCA test was applied. Patients with epilepsy evolution time of less than 1 year, patients with epileptic encephalopathies, patients with a previous diagnosis of cognitive impairment were excluded. Descriptive statistical analysis was carried out, as well as a correlation between the presence of cognitive deterioration and years with epilepsy and finally a logistic regression model.
Results: 55 patients were studied, mean age 32 (±13) years, female gender 50.9%, time of evolution of epilepsy 13 (±12) years. 61.8% (34) receive anti-seizure polytherapy, 38.2% (21) have controlled epilepsy. Regarding schooling, 72.7% (40) course more than 10 years. 80% (44) suffer from focal epilepsy, of which 68.8% (34) are temporal lobe epilepsy. Cognitive impairment with a MoCA score less than 26 was identified in 76.4% (42) of patients. The correlation between cognitive impairment and years of epilepsy was -0.179 (p=0.194). A binary logistic regression model was performed including age, years of epilepsy, gender, education, type of epilepsy, epilepsy control and temporal lobe epilepsy, finding statistically significant (p= 0.001) the presence of temporal lobe epilepsy.
Conclusion: Cognitive impairment was detected in a high percentage of patients with epilepsy, regardless of the time of evolution and epilepsy control, identifying the presence of temporal lobe epilepsy as a predictor. This highlights the importance of early screening in all patients with epilepsy, with the aim of performing early interventions seeking to stop the progression of cognitive decline in patients with epilepsy.

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Polypharmacy use frequency comparison of children and adolescents with focal epilepsy with mesial temporal sclerosis with and without intellectual disability

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Purpose: To compare the frequency of polypharmacy use in children and adolescents with focal epilepsy with mesial temporal sclerosis with and without intellectual disability.
Method: Retrospective, cross-sectional and analytical study. Children (from 6 years) and adolescents who attended the Pediatric Neurology service in the period from June 2021 to June 2022, who met the selection criteria (focal epilepsy with temporal mesial sclerosis), were divided into two groups: 1) with intellectual disability and 2) without intellectual disability. The frequency of use of monotherapy and polypharmacy was compared, considering polypharmacy from two or more antiseizure medication.
Results: A total of 310 files were reviewed, of which 54 met the selection criteria. The mean age was 12.38 (σ=3.32), in a range of 6 to 17 years, with the highest percentage being female at 50.9 % (n=27). The population was divided into two groups according to the presence (group 1, n=14, 26.4%) or absence (group 2, n=39, 73.6%) of intellectual disability to evaluate the frequency of polypharmacy in each, being 64.28 % (n=9) for group 1 and 35.89% (n=14 for group 2, with a range of use 1 to 3 antiseizure medication for group 1 and use of 1 to 4 in group 2. When comparing both groups through X2, a significant difference was not found (p=0.064).
Conclusion: Even a significant difference was not found, might be caused by the limited sample size. On the other hand, literature evidence for the adult population suggests a higher use of polypharmacy in the people with intellectual disability and epilepsy, in contrast with people with epilepsy and without intellectual disability.

Drug Therapy

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Relationship between antiseizure medication polytherapy and psychiatric comorbidities among people with epilepsy in Kilifi, Kenya

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Purpose: Pharmacological management of complex epilepsy may require use of more than one anti-seizure medication (ASM). While polytherapy may control seizures, risks, including

psychiatric problems have not been fully explored in Africa. We sought to examine the relationship between ASM polytherapy and psychiatric comorbidities among people with epilepsy (PWE) attending a community clinic in Kilifi, Kenya.
Method: We prospectively observed individuals attending an outpatient epilepsy clinic for patterns of ASM prescribing (mono- or polytherapy use) and investigated for any psychiatric diagnosis. The Psychosis Screening Questionnaire (PSQ) and the Patient Health Questionnaire Version 9 (PHQ-9) were used to assess for psychosis and depression, respectively. We conducted a cross-sectional logistic regression analysis (adjusting for age, sex, and residence) to: (i) determine factors associated with polytherapy; and (ii) examine impact of polytherapy and specific ASM use on psychiatric comorbidities, and the associated factors.
Results: Of the 3106 individuals, majority were on first generation ASM (3093 [99.6%]) with nearly a quarter (24.9%) on polytherapy. Carbamazepine co-administered with phenobarbital was the most common combination (9.4%). Children (aged <18 years; 40.5% vs 59.4%) were less likely to be on multiple ASM compared to adults. There was no difference between sexes. Polytherapy was associated with focal-to-bilateral seizures (adjusted odds ratio (aOR)= 1.46 [95% confidence interval:1.21-1.76]) and frequent seizures (aOR= 1.93 [1.41-2.63]). Further, combining ASM increased the likelihood of psychiatric problems (aOR= 3.44 [1.49-7.90]) but the association was not statistically significant for psychosis, (aOR= 1.41 [0.76-2.59]) or depression (aOR= 1.17 [0.53-2.56]) individually.
Conclusion: Many first generation ASMs usually do not have neuropsychiatric effects. Polytherapy, however, was associated with psychiatric comorbidities in our cohort. Initiation of rational polytherapy should therefore, be carefully considered and more research on the impact of ASMs on psychiatric comorbidities prioritised to better determine their role in influencing mental health in epilepsy, especially in the African context.

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Idiopathic generalized epilepsies: which seizure type is more difficult to control?

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Purpose: The purpose of the current study was to investigate that which seizure type is more difficult to be brought under control with antiseizure medication treatment in patients with idiopathic generalized epilepsy (IGE).
Method: This was a retrospective study of a large database of patients with epilepsy, which was built over more than a decade. All patients with a diagnosis of IGE, with at least 12 months of follow-up at our center, were studied at the epilepsy center at Shiraz University of Medical Sciences, Shiraz, Iran, from 2008 until 2022.
Results: 358 patients were included. The seizure types were generalized tonic-clonic seizures (GTCSs) (in 87.2%), myoclonic seizures (in 57.5%), and absence seizures (in 51.7%). Among patients who had GTCSs (N= 312), 160 patients (51.3%) became free of this seizure type. Among patients who had myoclonic seizures (N= 206), 122 patients (59.2%) became seizure-free. Among patients who had absences (N= 185), 127 patients (68.6%) became seizure-free. The

difference between the groups was significant (p= 0.0007). Receiving valproate was significantly associated with a myoclonus-free status (compared with other drugs).
Conclusion: The likelihood of seizure control is different for various seizures types in patients with IGE (seizure control is less likely for GTCSs and more likely for absences). Antiseizure drug efficacy should be considered along with other variables (e.g., sex) when selecting an appropriate ASM for a patient with IGE. Specifically designed clinical trials are needed to develop more efficacious and safe drugs to treat various syndromes of IGE.

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Composite findings from ten years (2014-2023) of The UK NHS Epilepsy and Intellectual Disability (EpID) NIHR database research register: using non-interventional observational datasets to evaluate the response of people with intellectual disability (PwID) to anti-seizure medications and treatments

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Purpose: Epilepsy is present in nearly 25% of People with Intellectual Disability (PwID) (general population – 1%) and associated with increased healthcare costs, morbidity and mortality, polypharmacy, treatment resistance and adverse effects. Prescribing practices remain primarily based on medication trials excluding PwID.

Specific objectives:
1. To evaluate the safety and efficacy for PwID and epilepsy of -
a. New (post 2005) Anti-Seizure Medications (ASMs)
b. Most common used ASM in UK – Levetiracetam (LEV)
2. To compare new ASMs to each other and LEV
Method: This UK NHS Ethics approved and NIHR adopted study applies a rigorous and systematic methodology for collecting and analysing large datasets of retrospective observational patient data, detailing real world responses to ASMs and treatments for PwID to generate level 2 evidence.
Patient data is collected on demographics, concomitant ASMs, dose, exposure length, adverse effects, retention rates, seizure type and frequency for the first 12 months of treatment. PwID and general population epilepsy data is compared. Only efficacy evaluation is provided here.
Results: In collaboration with 25 NHS Trusts acting as Data Collection Centres, 1185 research participants across five ASMs (Perampanel, Lacosamide, Eslicarbazepine, Brivaracetam and Levetiracetam) have been studied, comprising 477 PwID and 708 from the general population. 755 patients have been recruited for newer ASM arms and 430 for LEV.
Similar ASM responses are reported, along with higher comorbidity, adverse effects and slower titration for PwID. Group differences are reported as odds ratios estimated from logistic

regression models, with p >0.10 for association between ID group and efficacy for all ASMs. The database register allows for comparison with European collaborators and more specific recent focus on new treatments, including Epidiolex.
Conclusion: The EpID database register highlights an innovative research methodology. Findings have informed prescribing guidance for specific new ASMs, offering opportunities for comparison with established ASMs and evaluation of new treatments.

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Study 603: analysis of effectiveness and safety of perampanel in a multicentre, retrospective study in patients from Korea with focal-onset seizures who converted to monotherapy

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Purpose: We report final results from Study 603 that assessed effectiveness and safety of perampanel monotherapy following conversion from adjunctive therapy.
Method: Study 603 was a multicentre, retrospective study in Korean patients aged ≥12 years with focal-onset seizures (FOS). Data from perampanel-treated patients were categorised based on two periods: initiation of adjunctive perampanel and conversion to monotherapy. Primary endpoint: retention rates at 3, 6 and 12 months after conversion to monotherapy. Secondary endpoints: overall retention rates at 3, 6, 12, 18 and 24 months after perampanel initiation (adjunctive therapy or monotherapy); changes in seizure frequency/28 days and shifts in presence/absence of seizures between adjunctive therapy and monotherapy; safety. Retention rates and safety were assessed in patients with ≥1 dose of perampanel (Safety Analysis Set [SAS]); efficacy endpoints were assessed in patients from SAS who received monotherapy for ≥28 days (Full Analysis Set [FAS]).
Results: The SAS and FAS included 66 and 61 patients, respectively. Most common concomitant anti-seizure medication: levetiracetam (51.5%; n=34). Retention rates after conversion to monotherapy at 3, 6 and 12 months were 96.0%, 96.0% and 75.6%, respectively. Overall retention rates in patients after perampanel initiation at 3, 6, 12, 18 and 24 months were 100%, 98.3%, 95.9%, 92.6% and 92.6%, respectively. Mean seizure frequency/28 days (standard deviation [SD]) was 0.2 (0.79) during adjunctive therapy and 0.2 (0.64) during monotherapy; mean (SD) difference between adjunctive therapy and monotherapy was 0.0 (0.59; *P*=0.50). Shifts in presence/absence of seizures between adjunctive therapy and monotherapy were reported in 8/61 patients (present to absent, n=6; absent to present, n=2). Incidences of

treatment-emergent adverse events during adjunctive therapy and monotherapy were 6.1% and 3.0%, respectively.
Conclusion: Perampanel effectiveness was retained up to 12 months after conversion to monotherapy in Korean patients with FOS; no new safety signals were identified.

Funding: Eisai Korea Inc.

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Cluster analysis of a large dataset of patients with juvenile myoclonic epilepsy: predicting response to treatment

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Purpose: The purpose of the current study was to apply Two-step cluster analysis on a large dataset of patients with juvenile myoclonic epilepsy (JME). We hypothesized that there are distinct subgroups of patients with similar clinical characteristics. We also hypothesized that the seizure outcome is different between these clusters.
Method: This was a retrospective study of a prospectively developed database. All patients with a diagnosis of JME were studied at the epilepsy center at Shiraz University of Medical Sciences, Shiraz, Iran, from 2008 until 2022. The Two-Step cluster analysis (Schwarz's Bayesian Criterion) was applied to the whole dataset. In the next step, the seizure outcome was compared between the clusters of patients.
Results: Two hundred and ninety-five patients were included. Two-Step cluster analysis showed that there were two distinct clusters of homogeneous subgroups of patients with JME, presenting with more or less similar clinical characteristics, with a fair (0.4) silhouette measure of cohesion and separation. One hundred and eighty-one patients had a follow up duration of 12 months or longer at our center. Response to treatment at 12 months of follow-up was different between the clusters (as a trend): 43 patients (39.1%) from cluster 1 and 18 people (25.4%) from cluster 2 were free of all seizure types ($p = 0.076$).
Conclusion: The Two-Step cluster analysis identified two distinct clusters of patients with JME. Individuals with JME, who also have absence seizures, are less likely to enjoy a seizure free state with ASMs.

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Eslicarbazepine acetate monotherapy in post-traumatic epilepsy: a post-hoc analysis from a randomized, double blind, non-inferiority clinical trial (BIA-2093-311)

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Purpose: Post-traumatic epilepsy (PTE) is one of the most common and disabling sequelae of traumatic brain injury (BMC Neurology.2021,21:301). We aim to determine efficacy and safety/tolerability of eslicarbazepine acetate (ESL) monotherapy vs. controlled-release carbamazepine (CBZ-CR) in PTE patients.
Method: BIA-2093-311 was a phase III double-blind, randomized, parallel-group study, which demonstrated non-inferiority of ESL vs. CBZ-CR for seizure freedom (SF) rates (Epilepsia.2018,59(2):479-491). A post-hoc analysis was conducted for PTE vs. non-PTE patients to compare efficacy and safety.
Results: Of the 813 patients included, 525 (64.6%) had unknown aetiology and were excluded from the analysis. Of the remaining 288 patients, 80 (27.8%) had PTE (ESL, n= 35; CBZ-CR, n= 45) and 208 (72.2%) were non-PTE (ESL, n=97; CBZ-CR, n=111).
The average risk difference (ARD) between ESL vs. CBZ-CR arms in SF was similar in PTE and non-PTE groups, ARD= -5,0% (-27.0%,15.4%; 95%CI) and ARD = 5.7% (-7.6%, 18.6%), respectively.
In PTE group, treatment emerging adverse events (TEAEs) were reported by 82.9% and 73.3% of patients in ESL and CBZ-CR groups; related TEAEs: 42.9% (ESL) and 53.3% (CBZ-CR); related TEAEs leading to discontinuation: 11.4% (ESL) and 11.1% (CBZ-CR). In non-PTE group, TEAEs were reported by 81.4% and 81.1% of patients in ESL and CBZ-CR groups; related TEAEs: 39.2% (ESL) and 59.5% (CBZ-CR); related TEAEs leading to discontinuation: 10.3% (ESL) and 22.5% (CBZ-CR). No difference in TEAEs incidences were observed in PTE patients. In non-PTE group, ESL had lower discontinuation due to related TEAEs.
Conclusion: No significant differences were observed in SF and in safety/tolerability between ESL and CBZ-CR in PTE patients. In non-PTE patients, ESL was associated with fewer discontinuations due to related TEAEs although these results should be interpreted with caution due to small sample size and exploratory nature of analysis. ESL monotherapy may be an effective and well tolerated treatment option for patients with PTE.

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Inhibiting acid-sensing ion channel exerts neuroprotective effects in experimental epilepsy via suppressing ferroptosis

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Purpose: Epilepsy is a chronic neurological disease characterized by repeated and unprovoked epileptic seizures. Developing disease-modifying therapies (DMTs) has become important in epilepsy studies. Notably, focusing on iron metabolism and ferroptosis might be a strategy of DMTs for epilepsy. Blocking the acid-sensing ion channel 1a (ASIC1a) has been

reported to protect the brain from ischemic injury by reducing the toxicity of $[Ca^{2+}]_i$. However, whether inhibiting ASIC1a could exert neuroprotective effects and become a novel target for DMTs, such as rescuing the ferroptosis following epilepsy, remains unknown.
Method: In our study, we firstly explored the changes in ferroptosis-related indices, including glutathione peroxidase (GPx) enzyme activity and levels of glutathione (GSH), iron accumulation, and lipid degradation products-malonaldehyde (MDA) by collecting peripheral blood samples from adult patients with epilepsy. Meanwhile, we observed the expression of ASIC1a and mitochondria in the epileptogenic foci from patients with drug-resistant epilepsy (DRE). Next, we accessed the expression and function changes of ASIC1a and measured the ferroptosis-related indices on the *in vitro* 0-Mg^{2+} model of epilepsy with primary cultured neurons. Subsequently, we examined whether blocking ASIC1a could play a neuroprotective role by inhibiting ferroptosis in the epileptic neurons.
Results: Our study first reported significant changes in ferroptosis-related indices, including reduced GPx enzyme activity, decreased levels of GSH, iron accumulation, elevated MDA, and representative mitochondrial crinkling in adult patients with epilepsy. Furthermore, we found that inhibiting ASIC1a could produce an inhibitory effect similar to ferroptosis inhibitor Fer-1, alleviate oxidative stress response and decrease $[Ca^{2+}]_i$ overload by inhibiting the overexpressed ASIC1a in the *in vitro* epilepsy model induced by 0-Mg^{2+}.
Conclusion: Therefore, these data altogether indicated that inhibiting ASIC1a has potent neuroprotective effects via alleviating $[Ca^{2+}]_i$ overload and regulating ferroptosis on the models of epilepsy and may act as a promising intervention in DMTs.

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Characteristics of anti-seizure medication for epilepsy patients with autism spectrum disorder

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Purpose: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social communication and interaction and specific patterns of behavior, interests, and activities. In this study, we focused on the selection of anti-seizure medication (ASM) for epilepsy patients with ASD, which may affect their symptoms.
Method: We retrospectively reviewed the medical records of patients diagnosed with ASD who regularly visited our epilepsy clinic. We exclude patients with specific syndromes causing both ASD and epilepsy, such as Tuberous Sclerosis Complex. Data regarding demographic characteristics, clinical features, classification of epilepsy syndromes, electroencephalogram findings, anti-seizure medication, and adverse events were recorded.
Results: Twenty-four patients (14 males, 10 females) were enrolled, with a median age of 12.5±3.4 years old (ranging from 6 to 20 years). The classification of epilepsy was generalized epilepsy in 4, focal in 14 and unknown in 5 cases. The localization of interictal discharges in

electroencephalogram was observed in 8 cases as focal, 5 as diffuse, 6 as focal and diffuse, and normal in 5.
As the first-line ASM, 13 cases were administrated with valproate, 6 with carbamazepine, zonisamide, perampanel, and lacosamide in 1 case each. Two cases were observed without ASM. Eight cases received the second ASM, and 5 received the third. In two cases received levetiracetam and benzodiazepines were discontinued due to aggression or psychiatric symptoms.
The ASMs that the cases received at the last visit were valproate in 11, carbamazepine in 5, lacosamide in 4, perampanel in 2, zonisamide, lamotrigine, topiramate, and levetiracetam in 1 case. Thirteen cases (54%) were monotherapy and 2 cases discontinued their AMS due to seizure remission.
Conclusion: Mood stabilizers such as valproate and carbamazepine are often used for epilepsy patients with ASD and are well tolerated. There was a tendency not to select drugs that had a large effect on emotional and behavioral abnormalities.

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12-Month effectiveness and tolerability of brivaracetam in patients with epilepsy switching from levetiracetam vs other antiseizure medications in the real-world: subgroup data from the international EXPERIENCE pooled analysis

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Purpose: Assess effectiveness and tolerability of brivaracetam (BRV) in patients switching from levetiracetam (LEV) and patients switching from other antiseizure medications (ASMs).
Method: Subgroup analysis of EXPERIENCE/EPD332, a pooled analysis of patient-level data from patients with epilepsy initiating BRV in clinical practice. ≥50% seizure reduction from baseline, seizure freedom (SF; no seizures within 3 months prior to timepoint), continuous SF after baseline (CSF; no seizures from baseline) at 3, 6 and 12 months, and treatment-emergent adverse events (TEAEs) since prior visit were assessed. Patients with missing data after BRV discontinuation were considered non-responders and not seizure free.
Results: 709 (43.8%) patients switched from LEV and 887 (54.8%) switched from other ASMs. Most patients switching from LEV/other ASMs had focal-onset seizures at baseline

(92.7%/91.9%). Patients switching from LEV/other ASMs showed similar epilepsy duration (median: 18.0/17.0 years; n=694/864), seizure frequency at index (median: 4.0/4.3 seizures/28 days; n=537/807), and number of prior ASMs (mean [SD]: 5.0 [3.7]/6.0 [3.9]; n=709/887). At index, median BRV dose was 100 mg/day (Q1–Q3, 50.0–200.0, n=699) in patients switching from LEV and 50 mg/day (Q1–Q3, 50.0–100.0, n=869) in patients switching from other ASMs. Median BRV duration was 353.1/337.4 days (n=703/878). ≥50% seizure reduction from baseline, SF, and CSF were similar in patients switching from LEV/other ASMs at all timepoints (12 months: ≥50% seizure reduction, 34.6%/38.3% [n=295/512]; SF: 14.9%/13.9% [n=484/596]; CSF: 11.4%/10.9% [n=484/596]). At 12 months, incidence of TEAEs was similar in patients switching from LEV/other ASMs (9.5%/9.1%; n=525/662); somnolence (3.0%/1.7%) was the most common TEAE. Incidence of irritability was 1.3%/0.5%, and aggression was 0.8%/0.3%. BRV discontinuations in patients switching from LEV/other ASMs were 32.0%/35.8%; n=706/885).
Conclusion: Effectiveness of BRV was similar in patients switching from LEV to BRV versus patients switching to BRV from other ASMs. BRV was well tolerated in both groups.

Funding: UCB Pharma-sponsored

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PRAX-628: A Next Generation Functionally Selective Small Molecule with Potent Anticonvulsant Activity

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Purpose: Gain-of-function (GoF) pathogenic variants in voltage-gated sodium channel (Na_V) genes can increase sodium channel activity leading to neuronal hyperexcitability and severe developmental and epileptic encephalopathies (DEE). PRAX-628 is a novel activity dependent sodium channel (I_{Na}) blocker, which we have previously shown inhibits peak I_{Na} with greater activity dependence compared to standard-of-care carbamazepine (CBZ) and lamotrigine (LTG). Here we further define its in vivo efficacy and tolerability profile in mice.
Method: The anticonvulsant activity of PRAX-628 (0.3-10 mg/kg) was assessed using the maximal electroshock seizure (MES) assay in outbred CD-1 mice. Effects of PRAX-628 (3-20 mg/kg) on spontaneous locomotor activity (sLMA) were measured to assess tolerability. The protective index (PI) of PRAX-628 was determined as the ratio of plasma concentrations in sLMA (TC_{50}) to MES (EC_{50}). The effects of CBZ and LTG were also assessed using MES (3-30 mg/kg and 1-10 mg/kg, respectively) and sLMA (30-96 mg/kg and 20-63.4 mg/kg, respectively), and their corresponding PIs computed. The concentration of PRAX-628 in terminal plasma and brain samples was measured using mass spectrometry.
Results: PRAX-628 (10 mg/kg) completely blocked evoked seizures (MES ED_{50} 0.67 mg/kg, brain EC_{50} 67.2 ng/g) without affecting sLMA (TD_{50} 10.27 mg/kg, plasma TC_{50} 1123 ng/g; PI 16.7). In contrast, CBZ and LTG had PIs of 5-6x; full anticonvulsant efficacy with CBZ or LTG was not achieved without reducing sLMA.
Conclusion: PRAX-628 exhibited markedly improved preclinical tolerability compared to standard of care Na_V blockers, potentially due to its improved activity dependent inhibition of

peak I_{Na}. The profile of PRAX-628 may translate into well-tolerated efficacy in epilepsy as well as other indications caused by neuronal hyperexcitability.

Funding: Praxis Precision Medicines.

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Long-term effect of Cenobamate in a cohort of therapy refractory adult patients with different types of epilepsies

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Purpose: To investigate retention rate of Cenobamate (CNB) in different epilepsy syndromes at a tertiary epilepsy center with a follow-up of 12 months minimum
Method: We sampled all data of therapy refractory epilepsy patients who got CNB in 2021 in our tertiary epilepsy center and analyzed effect and side effect in 120 patients after 12 month treatment minimum. We calculated Kaplan Meier retention rates for that group.
Results: We investigated 120 patients (pts) 68 men, 52 women with a mean age of 40.4 years (17-77). We saw pts with multifocal epilepsies (11), generalized epilepsies (12, LGS) and focal epilepsies (97) due to genetic causes (11), structurell lesions (52) autoimmun induced (12) and unclear (24). Comedication was: Lamotrigine (49) Valproat (41) Clobazame (35) Brivaracetam /Levetiracetam (37) Lacosamid (15), Oxcarbazepine (15) Perampanel (7) Zonisamide (5) Stiripentol (5) Topiramat (4) Phenobarbital (2) Rufinamide (1), Felbamate(1), Carbamazepine (1). Most of the pts got 2 oder 3 ASM in comedication. CNB was given to a monotherapy in 10 pts, to duotherapy in 57 pts, to 3 ASM in 39 pts, and to more than 3 ASM in 14 pts, 7 with VNS. Mean dosage of CNB was 220 mg/d (50-400 mg/d).Retention rate after 6 month was 80 %, after 12 month 70%. Side effects were seen in 55 pts, in 20 pts yGT arise, in 2 pts DRESS and in more than 10 dysarthria, obstipation, irritability, agressivity and double vision.12 became seizure free, 65 got a seizure reduction > 50%, 21 had no effect and 23 stopped treatment. Subanalysis of 44 pts with mental handicap reveals a less good response, only 4/44 pts got seizure-free.
Conclusion: CNB is a safety and efficious ASM, 10% of therapy resistant patients got seizure free, retention rate was 70 %. In pts with multifocal and generalised epilepsies CNB seems to be less effective.

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XEN1101, a novel potassium channel modulator: interim data from an ongoing, long-term, open-label extension of a phase 2b study (X-TOLE) in adults with focal epilepsy

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Purpose: XEN1101 is a novel, potent, selective KCNQ2/3 (K_V7.2/7.3) potassium channel opener in development for the treatment of focal onset seizures (FOS). We report interim data from an ongoing, long-term, open-label extension (OLE) of a phase 2b study (X-TOLE) of XEN1101 in adults with focal epilepsy.
Method: After the 2-month, double-blind period (DBP), eligible patients began the OLE at 20 mg once daily in the fed state. The primary efficacy outcomes were median percentage change (MPC) in monthly FOS frequency from DBP baseline and monthly response rate (≥50% reduction from DBP baseline in monthly FOS frequency). Safety was assessed as severity and frequency of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs), clinically significant changes in laboratory findings and other measures.
Results: 275/285 patients (96.5%) completed the DBP and entered the OLE. At time of analysis cut-off, 188 and 111 patients had been treated in the OLE for ≥12 and ≥18 months, respectively. For ongoing OLE patients, monthly MPC reductions ranged from 60-90% from DBP baseline and were maintained at 80%–90% in OLE study months 12-18. Higher reductions were observed for patients receiving 1-2 antiseizure medications (ASMs) at baseline vs those receiving 3 ASMs. 10.5% of patients (29/275) achieved seizure freedom for any consecutive ≥12-month duration, and 17.5% (48/275) were seizure free for any ≥6 consecutive months. Most common TEAEs were dizziness (20.7%), headache (13.5%), COVID-19 (11.6%), and fall (11.3%).
Conclusion: XEN1101 20 mg QD yielded long-term efficacy in this interim analysis with sustained monthly reduction in seizure frequency from DBP baseline. XEN1101 continues to be generally well-tolerated in the OLE: AEs are consistent with previous results and other ASMs, and no new safety signals were identified.

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Quality-of-life improvements in adults with focal onset seizures treated with XEN1101 in an ongoing, long-term, open-label extension of a phase 2b study (X-TOLE)

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Purpose: XEN1101, a novel, potent, selective KCNQ2/3 (K_V7.2/7.3) potassium channel opener,

showed a dose-dependent, statistically significant, and rapid-onset seizure frequency reduction in a randomized, double-blind, placebo-controlled phase 2b study (X-TOLE) in adult patients with ≥4 focal onset seizures (FOS) per month. Of the 285 patients completing the double-blind period (DBP), 275 (96.5%) enrolled in the open-label extension (OLE). At 12 months in the ongoing OLE, patient retention was 68% (n=188), and monthly FOS median reduction was 80%. Across all ongoing X-TOLE OLE patients, 29 (10.5%) were seizure free for ≥12 consecutive months. Here we report on quality-of-life improvements in the XEN1101-treated adults with FOS in the X-TOLE OLE.
Method: Eligible patients transitioned from the DBP to the OLE at 20 mg once daily in the fed state. The Quality of Life in Epilepsy-31 scale (QOLIE-31) was completed at 3-month intervals and was compared to the DBP baseline assessment at 12 months. Minimally important change thresholds in QOLIE-31 scores were applied to the overall group (OG) and the group that was seizure-free for 12 consecutive months (SFG; n=29).
Results: At 12 months, QOLIE-31 subscale scores met the threshold for improvement in the OG and SFG as follows: seizure worry mean change (11 and 26 points), social functioning (8 and 21 points), and medication effects (6 and 22 points), respectively. Overall quality-of-life change (10 points) and total QOLIE-31 total score (12 points) met the threshold for improvement in the SFG only.
Conclusion: Several QOLIE-31 domains showed important changes. Improvements in seizure worry and social functioning were seen across patients, with enhanced scores in the SFG. The overall improvement in medication effects, which was accentuated in the seizure-free patients, highlights a clinically relevant group who maximally benefited from XEN1101 for seizure reduction while also perceiving an improvement in drug tolerability.

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Pulse intravenous methylprednisolone in epileptic encephalopathy: an extended follow up

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Purpose: Subjects who were randomized to receive pulse IV steroids in a completed RCT *(Rangarajan et al. JNNP 2022, Epub ahead of print)* were subsequently follow up to assess the duration of sustained response after cessation of treatment.
Method: Forty subjects (M:F=33:7) had received treatment with steroids in the trial and 5 were lost for further follow up. Seventeen children received an extended regimen of pulse IV steroids (Range: 5-10 monthly pulses). The duration of response (sustained ≥50% reduction in seizure frequency) after stopping treatment was recorded. Adverse effects if any were also

enquired on follow up.
Results: Thirty-five subjects who continued to follow up after the trial/last dose of steroid pulse had sustained response ranging from 0-24 months (mean: 8.3 ± 5.6 months). Immediate loss of response upon stopping steroids was detected in 2 patients. Most children (n=25) had sustained response for at least 6 months after completing steroid pulses and 16 of these patients had received extended pulse. This difference was statistically significant (p=0.007) The mean duration of sustained response was higher in the extended pulse regimen group (11.1 ± 6.5 months) compared to the standard regimen (5.6 ± 3.0 months) (95% CI 2.0-8.9 months; p=0.002). No steroid induced adverse effects were noted.
Conclusion: Sustained remission was noted in 71% of subjects for atleast 6 months after receiving steroid pulses. This effect appeared to increase in duration if pulse steroid regimens are extended without apparent serious adverse effects. Pulse steroid therapy appears to be a safe and effective treatment to reduce seizure frequency in epileptic encephalopathy.

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Dimethyl fumarate (DMF) repurposing: the antiepileptogenic and disease-modifying effect of DMF in temporal lobe epilepsy

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Purpose: Many epilepsies are acquired conditions following an insult to the brain. The generation of reactive oxygen species (ROS) and induction of oxidative stress are common sequelae of such brain insults and have been shown to contribute to neuronal death and the development of epilepsy. Here, we propose to use the highly selective, FDA-approved, orally available, and brain-penetrant Nrf2 activator dimethyl fumarate (DMF), to increase the endogenous antioxidant system through Nrf2 activation to prevent the development of seizures following SE, and also for modifying the severity of chronic epilepsy.
Method: We used the Kainic Acid-induced Status Epilepticus (KA-SE) model in rats. The expression of Nrf2 and downstream genes was tested by PCR and western blot analysis. Rats were treated with DMF shortly after SE for the antiepileptogenic effect, or 10-12 weeks following SE after confirming chronic epilepsy. The development of seizures was monitored using video-ECoG recordings for up to 18 weeks.
Results: We first demonstrated that DMF increases the expression of Nrf2 and related genes in both the cortex and the hippocampus. We then found that by increasing the Nrf2 activity, DMF attenuated SE-induced neuronal cell death in the hippocampus of treated animals. When administered over 7 days following SE, DMF significantly decreased the seizure frequency and the total number of seizures compared to vehicle-treated animals.
Importantly, we found that treatment initiated well after epilepsy diagnosis, i.e., 12 weeks after SE, DMF decreased the seizure frequency and the total number of seizures post-treatment.

Conclusion: DMF, via the activation of Nrf2, increases the endogenous antioxidant system in the brain after SE, attenuates neuronal damage, and prevents the development of epilepsy. Our results with DMF suggest that Nrf2 activation is disease-modifying because the treatment effect long outlasted the circulating drug's presence.
DMF, an FDA-approved Nrf2 activator, holds great promise of repurposing for epilepsy.

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Safety overview of post-marketing psychiatric disorders reported in patients treated with Eslicarbazepine Acetate

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Purpose: Eslicarbazepine Acetate (ESL) is a once-daily anti-seizure medication approved in Europe and North America as monotherapy or adjunctive therapy in patients with focal seizures with or without secondary generalisation. Epilepsy has a high risk of psychiatric comorbidities, which have been associated with poorer health outcomes, increased health care needs, decreased quality of life and greater social exclusion.
This study aims to review all psychiatric adverse events (AEs) reported in patients under ESL therapy, received by the Marketing Authorization Holder (MAH) from post-marketing surveillance.
Method: ESL global safety database was searched by the MAH for valid post-marketing reports from launch (2009) to November 2022. AEs corresponding to the system organ class 'psychiatric disorders' according to version 25.1 of Medical Dictionary for Regulatory Activities were included. Expectedness was assessed based on the most recent Reference Safety Information.
Results: 849 AEs were collected from 539 valid safety reports. Patients' median age was 47 years (min. 3, max. 97; unknown age: 177), with 312 (57,9%) female patients (unknown gender: 18). Most were spontaneous reports (449; 83,3%), followed by reports from studies (77; 14,3%) and literature reports (13; 2,4%). The 5 countries with most reports were: United States of America (335; 62,2%), France and Germany (each 48; 8,9%), Spain (47; 8,7%) and the United Kingdom (22; 4,1%). 221 AEs were classified as serious (26,0%). The 5 most common 'Preferred Terms' (PT) were confusional state (77; 9,1%), insomnia (63; 7,4%), suicidal ideation (57; 6,7%), depression (53; 6,2%) and aggression (43; 5,1%); suicidal ideation and aggression were unexpected.
Conclusion: Most of the 'Psychiatric disorders' AEs were non-serious. Within the 5 most reported PTs, the majority were expected, in line with the known safety profile of ESL. No new relevant safety concern was identified. ESL maintains an adequate benefit-risk profile.

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Significant improvements in SEIzure InterVAL (time between seizure clusters) across time: post hoc analysis of a long-term, open-label safety study of diazepam

nasal spray

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Purpose: Metrics for effectiveness of seizure-cluster rescue therapies across multiple days are lacking. We explored a novel measure of effectiveness, SEIzure interVAL (SEIVAL; time between seizure clusters) in a long-term safety study of diazepam nasal spray (Valtoco®), which is approved for acute treatment of seizure clusters in patients with epilepsy aged ≥6 years. This analysis characterized time between seizure clusters in patients using diazepam nasal spray rescue therapy.
Method: A post hoc analysis of a long-term, open-label, repeat-dose safety study of diazepam nasal spray in patients aged 6–65 years with epilepsy and frequent seizure clusters evaluated SEIVAL across 4 consecutive 90-day periods (total 360 days). Paired *t* tests assessed statistical significance.
Results: Of 175 enrolled patients, 163 received ≥1 dose of diazepam nasal spray, and 120 had SEIVAL data in period 1 and another period. A consistent cohort (n=76) had data in all 4 periods. In the 120 patients, mean SEIVAL increased from 14.8 to 35.8 days (Period 1 to 4). In the consistent cohort, mean SEIVAL increased from 13.9 to 26.8 days ($P \leq 0.001$). In pediatric patients (age 6–17 years, n=32), mean SEIVAL increased from 13.0 to 25.9 days ($P=0.02$). In adults (n=44), mean SEIVAL increased from 14.6 to 27.5 days ($P=0.01$). Mean SEIVAL also increased in patients with (n=56; from 13.9 to 25.8 days) and without (n=20; from 14.1 to 29.6 days) changes in concomitant antiseizure drug (ASD) therapy during the study.
Conclusion: Across 12 months, a statistically significant change in SEIVAL was observed, which may reflect a beneficial effect of intermittent rescue therapy with diazepam nasal spray and appears to be independent of age or changes in concomitant ASDs. These findings may reflect patient behavior or other factors, including a change in the underlying pathophysiology of seizure clusters; these hypotheses warrant further study.

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Quality of life in Mexican patients with epilepsy who consume cannabidiol

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Purpose: Measuring the quality of life of patients with refractory epilepsy (more than 5 seizures per week despite taking two antiepileptic drugs at adequate doses) who consume cannabidiol.

Method: Between March/2018 and April 2019, we conducted an online survey with 57 Mexican patients (quoli48 quality of life survey in addition to semi-structured interview).
Results: 43% were male, with an average age of 12.4 years, all taking Cannabidiol 100% (Real scientific Hemp Oil RSHO-X/RHOIL). The age of onset of epilepsy was 4.5 ± 3 years and all the patients showed 2 or more types of epileptic seizures (generalized tonic-clonic 66%, focal 22%, myoclonic 39%, epileptic spasms 37%) with a frequency of tens a day. The most used antiepileptic drugs are: valproic acid 68%, levetiracetam 67%, vigabatrin 30%, lamotrigine 26%, clobazam 26%, lacosamide 23%, topiramate 14%. The 7% received vagal stimulation and 7% were callosotomized.
The 75% of patients received information about CBD from their doctor (12% via the internet). The average time between diagnosis and the use of CBD was 7 ± 6 years, the duration of treatment was 12 ± 6 months, with a dose of 4 mg/Kg (7-10 mg/kg for children and 100 mg/day for adults).
The average of reduction of seizures in auto-report was 67%. Better quality of life was reported by 62%, improved behavior by 50% and quality of sleep by 48%. The results of the quoli48 test were lower than those reported in patients with epilepsy in other countries.
Conclusion: Cannabidiol (RH OIL) improves the quality of life of patients with refractory epilepsy.

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In-silico investigation of anti-seizure drug candidates: criteria for screening and prioritization of candidates in repurposing and novel compound trials

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Purpose: We have recently shown that contemporary small-molecule drug design tools suffer from shortcomings in prediction of clinical efficacy of ASMs, partly because their characteristics differ from those of other CNS drugs. We pursued design of a desirability score for in-silico screening of ASM candidates.
Method: We performed large-scale statistical analyses of marketed ASMs in comparison with multiple groups of small-molecule drugs: failed ASM candidates with studies supporting lack of clinical efficacy, “abandoned” candidates for which no new data have been published by the investigating party in the last 5 years, drugs which permeate the BBB, and a general cohort of marketed drugs. Drug groups were compiled from multiple sources, including a systemic literature review, drug catalogues, and ClinicalTrials.gov data. The multiple testing problem and potential bias introduced by design trends were taken into account in the statistical analyses. The resulting novel statistical insights, along with structure-activity relationship domain knowledge, guided development of the desirability score model.
Results: An initial desirability score function classified small-molecule compounds into high-, medium-, and low-desirability groups based on physiochemical properties. Among a cohort of

~1600 small-molecule non-prodrug marketed compounds, approximately 45% were classified as low-desirability. All marketed ASMs were either of high-desirability (87%) or medium-desirability (13%), achieving high sensitivity. Furthermore, the model classified 60% of drugs with proven lack of clinical anti-seizure efficacy as low-desirability compounds. The model demonstrated additional discriminatory power for clinical antiseizure efficacy in comparison with contemporary CNS drug design tools, both in sensitive and specificity.
Conclusion: We built an open access calculator that enables investigators to rapidly assess compatibility of compounds with the suggested screening criteria. The presented desirability function may be used for evaluating ASM candidates. In silico candidate prioritization can reduce human harm, minimize unnecessary clinical trials and animal use, and lower the cost of ASM introduction into the clinic.

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Corticosterone improves early traumatic brain injury outcomes linked to post-traumatic epilepsy

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Purpose: Patients with traumatic brain injury (TBI) are at a higher risk for developing post-traumatic epilepsy (PTE), but the underlying mechanisms are not well understood and there remains an unmet need for protective therapies and reliable biomarkers. Our research suggests that blood-brain barrier dysfunction (BBBD) and TGFβ signaling play a role in PTE development. Using a rodent TBI model, we found that 50% of rats were susceptible to TBI: showing a greater decline in Neurological Severity Score, increased acute convulsions, and BBBD compared to resilient animals. They were also more likely to develop PTE. Notably, resilient rats had a 10-fold increase in corticosterone post-injury compared to susceptible rats. This led us to hypothesize that increased corticosterone post-injury can promote blood-brain barrier repair by blocking TGFβ signaling in endothelial cells. Therefore, our study aims to explore the roles of (i) corticosterone in BBBD repair, (ii) TGFβ signaling in epileptogenesis, and (iii) drug therapies for preventing PTE susceptibility.
Method: We used adolescent male Sprague Dawley rats (n=187) and collected behavioral and electrophysiological data via our established rodent TBI model. We also analyzed corticosterone levels in serum and feces and quantified BBBD using imaging assays.
Results: Our data showed that susceptible rats had higher incidence of acute convulsions and PTE compared to resilient animals (P=0.0053). Surprisingly, electrophysiological recordings showed that seizures were not the cause of acute convulsions. Moreover, susceptible rats had lower corticosterone levels after TBI (P=0.03), but similar ACTH levels to resilient rats. Lastly, injection of corticosterone or TGFβ blockers protected against acute neurological deterioration ($p=0.0056$ and $p<0.001$) and prevented PTE ($p<0.05$).
Conclusion: Our study suggests that corticosterone plays a key role in TGFβ-induced BBBD,

making it a potential biomarker of TBI and PTE susceptibility. Further research should investigate the effectiveness of corticosterone and TGFβ blockers as treatment modalities for PTE.

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A mirroring clinical practice study of perampanel in adults and adolescents (AMPA): assessment of impact of perampanel on seizure control, sleep and quality of life

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Purpose: The AMPA Study (NCT04257604; Study 501) was a prospective, observational 12-month study to evaluate the effectiveness, safety and quality of life (QoL) of adjunctive perampanel in routine clinical practice in Italy. Here, we present a post hoc analysis in a subgroup of patients (≥18 years) with excessive daytime sleepiness at baseline, stratified by the End-of-Study Epworth Sleepiness Scale (ESS) score.
Method: Patients with insufficiently controlled focal-onset seizures, with/without focal to bilateral tonic-clonic seizures, receiving 1–3 anti-seizure medications were prescribed adjunctive perampanel in line with the approved indication. Endpoint measures at Month 12 included ESS scores (<11 [normal daytime sleepiness] vs ≥11 [excessive daytime sleepiness]), median percent change in seizure frequency per 28 days, QoL scores (assessed by the QoL in Epilepsy-31-Problems questionnaire [QOLIE-31-P]) and treatment-emergent adverse events (TEAEs).
Results: Of 234 patients who received adjunctive perampanel (Safety Analysis Set), 28 had a baseline ESS score ≥11 (excessive daytime sleepiness) and were included in this analysis. Of those, 17 (60.7%) patients reported normal daytime sleepiness at End of Study relative to baseline and 11 (39.3%) patients reported excessive daytime sleepiness. Median reduction from baseline in seizure frequency at Month 12 was 84.6% (95% confidence interval 58.8, 100.0) for patients with normal daytime sleepiness, and 46.8% (13.2, 89.0) for patients with excessive daytime sleepiness. At Month 12, patients with normal daytime sleepiness reported stable or improved QoL scores, whereas those with excessive daytime sleepiness reported worsening QoL scores. TEAEs were reported by 52.9% vs 72.7% of patients with normal vs excessive daytime sleepiness at Month 12, respectively.
Conclusion: In patients from the AMPA Study with excessive daytime sleepiness at baseline, improvement in End-of-Study ESS score appears to correlate with improvements in seizure control, QoL and tolerability.

Funding: The AMPA Study was funded by Eisai S.r.l.

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Cenobamate in real-life setting: final outcomes of an expanded access program

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Purpose: Early real-life experience of antiseizure medication (ASM) is provided by Expanded Access Program. This work reports final outcomes of EAP with cenobamate (CNB) in a large series of patients with epilepsy in Spain.
Method: It is a multicenter, retrospective, observational study in 14 hospitals. Inclusion criteria for EAP were 1) older than 18 years; 2) focal seizures; 3) EAP authorization.. The source of data was patient clinical records and time-points analyzed were baseline, 3 months and 6 month and 12 months. Patients with less than 3 months of follow-up were excluded from the analysis.
Results: A total of 170 patients were included. At baseline, mean epilepsy duration was 26 years and mean number of seizures/month was 23. Mean (range) number of prior ASM was 12,1 (4-20) and mean number of concomitant ASM was 3,2. The mean dosage/day was 175,8 mg (3 months) , 200,2 mg (6 months), and 250 mg (12 months). The retention rate was 98,2% at 3 months (167/170), 94,5% at 6 months (120/127) and 87% at 1 year (40/46). At last available visit seizure-freedom was 13.3%, ≥90% responder was 27,9%, ≥75% responder was 45.5% and ≥50% responder was 63%. The responses were maintained regardless of the prior number of ASM and concomitant ASM. The number of concomitant ASM was reduced in 44,7% of the patients (particularly carbamazepine, clobazam and lacosamide). The cumulative percentage of patients with adverse events and those that led to discontinuation were 68,2% and 3.5% at 3 months, 74,1% and 4.1% at 6 months and 74,1% and 4.1% at 12 months. The most frequent AE were somnolence, dizziness, memory disturbances and ataxia.
Conclusion: The outcomes in a refractory population treated with CBM showed a high response regardless of prior and concomitant ASM. AE were reported in high proportion of patients but few of them led to discontinuation

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The evaluation of the effect of different generation anticonvulsants on bone mineral density: preliminary study results

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Purpose: To study the effect of different generation antiepileptic drug (AED) on bone mineral density (BMD) in patients epilepsy (PE) aged 20–50 years with antiepileptic therapy for a long time
Method: We studied 38 PE (15 men (39.5%) and 23 (60.5%) women), aged 20 to 48 years (SD 34±7,36) without somatic and endocrinological pathology. All patients had an diagnosis of epilepsy and received AED therapy for at least three years. The BMD was examined by Quantitative Computed Tomography (QCT) at three points (L1, L2 and the femoral neck).
Results: The decrease of the BMD were find in 13 (34,2%) patients, in 6 (15,8% of all) men and 7 (18,4% of all) women. 11 PE had T-score (BMD) -1.59 SD (osteopenia) and 2 PE had T-score -2.85 SD (osteoporosis). The 1st group - 17 PE taking «first generation» AEDs, the 2nd group - 21 PE with «second and third generation» AEDs. The decrease of the BMD was observed in 47.1% PE of 1st group and 23.8% PE of the 2nd group (ϕ=1,514; p>0.05).
Conclusion: The pilot results of the study showed the decrease of the BMD in PE with long-term history of antiepileptic therapy. When comparing the degree of influence of the different generation AEDs on the state of mineral metabolism (BMD) in patients with epilepsy under 50 years old, it was not possible to identify significant differences, which indicates the need for further, longer and a large-scale study of the impact AEDs.

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One-year safety, efficacy, and retention of cannabidiol (CBD) as add-on therapy in patients with refractory epilepsy

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Purpose: We aimed to assess the real-life safety, efficacy, and retention of Cannabidiol (CBD) as palliative adjunctive therapy in Cypriot patients with refractory epilepsy of any etiology.
Method: Thirty adult patients (including two with Tuberous Sclerosis and two with Lennox-Gastaut syndrome) followed at a tertiary epilepsy center were studied retrospectively for one year after the addition of CBD in their Antiseizure Medications (ASMs). CBD dose ranged between 5-20 mg/kg/day. Data on seizure frequency, seizure intensity, treatment-emergent Adverse Events (AEs), and overall CBD effect were obtained from medical files and patient and caregiver diaries.
Results: At the time of CBD initiation, the mean illness duration was 26 (9-58) years and patients were experiencing a mean of 16 (1-60) seizures per month. Patients had failed a mean of 8 (3-12) ASMs and combinations thereof. CBD was added to a mean of 4 (1-6) concomitant ASMs. Fourteen patients (47%) were under treatment with Vagus Nerve Stimulation (VNS).

Twenty-five patients (83%) completed twelve months of treatment. A mean reduction of 32% in monthly seizure frequency was observed compared to baseline (p= 0.032).
Five patients (17%) discontinued CBD treatment: three patients due to AEs (transaminase elevation, somnolence, and aggression) and two patients due to seizure frequency increase. CBD retention rate was 83%.
Fourteen patients (47%) responded to CBD treatment achieving seizure reduction of ≥50% sustained for 12 months, whilst 3 patients (10%) became seizure-free. Subjective improvement in seizure frequency, seizure intensity, and/or patient behavior was reported by 70% of caregivers.
None of the baseline characteristics was found to affect the probability of patients responding to CBD treatment.
AEs were reported by thirteen patients (43%). Most frequently reported were somnolence (13% of patients) and irritability/aggression (10% of patients).
Conclusion: Cannabidiol was proven to be a safe and effective addition to anti-seizure medications in our population of highly pharmacoresistant patients.

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Availability of perampanel monotherapy in self-limited epilepsy with centro-temporal spikes

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Purpose: Perampanel (PER) is an antiepileptic drug of non-competitive agonist of AMPA receptor, which are postsynaptic ionotropic excitatory receptors with glutamate binding sites. Since it is administered once a day before sleep, good compliance can be expected with monotherapy. In this study, we investigated availability of PER monotherapy in Self-Limited Epilepsy with Centro-Temporal Spikes (SeLECTS).
Method: Subjects aged 4 years and older who were diagnosed with SeLECTS between April 2020 and March 2022 and used PER as first-line therapy were enrolled in this study. Diagnosis of SeLECTS was performed based on clinical seizure types and interictal EEG findings. Informed consent was obtained from parents in all cases. Medical information was collected by retrospective review of medical records.
Results: Ten cases were enrolled in this study, and the age of onset was 4-8 years old. Interictal EEG before PER administration showed frequent centrotemporal spikes during sleep in all cases. Eight had spikes even in awake stage, and 2 had a generalized spike and wave complex. All cases had 2 or more seizures before PER administration. The maintenance dose of PER was 1-4 mg per day, and the maximum steady-state PER blood concentration was 141-1520 ng/mL. PER was continued in 9 cases, and the number of seizures after starting PER was 0-4 (median 1). In one case, after the seizure remission of 9 months with PER, recurrence of weekly seizures appeared and PER discontinued. No noteworthy adverse effects were observed, and no exacerbation of interictal EEG was seen after PER administration.

Conclusion: Although SeLECTS characterized by seizures limited during sleep and could manage without medication, optimization of treatment is difficult due to concerns about decreased cognition, and refractory seizures. PER monotherapy is expected to be a good indication because it is administered once daily with good compliance without serious adverse effects.

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Difficulty of anti-seizures medications selection in female with juvenile myoclonic epilepsy(JME)

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Purpose: To review current treatment of JME between period 15/06/2007 to 15/06/15/06/2022.
Method: Search was done in Pubmed . All the articles published in the last 15 years were included.
Results: FDA,NICE and Cochrane all advice against sodium valproate due to teratogenic and neuro development side effects unless the suggested leverictam , lamotrigine have failed to control the seizures and the patient is informed of the risks .Topiramate not strongly suggested.Perample is proposed but not specifically for JME in a retrospective study.Cases with resistant JME and underlying psychiatric problems which are common in females were not addressed though such patients may have exacerbation of his symptoms exacerbated by leverictam.
Conclusion: There is yet no evidence guidelines to find the appropriate treatment for females with JME.The long term effect on newborn have not been assessed in leverictam ,lamotrigine or perampanel.Zonzomide was reported in few case reports .
I think there is still a place for clonazepam as an adjunct therapy in patients with frequent myoclonus, anxiety, tremors and sleep difficulties .Also in patients receiving lamotrigine with frequent jerks and it needs to be further explored. Sodium valoproate in dose not exceeding 400 mg may be prescribed in resistant cases with risks explained to patients.

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Successful treatment of Lacosamide as adjunctive therapy for juvenile myoclonic epilepsy: a case series

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Purpose: We aimed to evaluate the long-term efficacy of adjunctive lacosamide (LCM) ther-

apy for uncontrolled generalized tonic-clonic seizures (GTCS) in patients with Juvenile myoclonic epilepsy (JME).
Method: A retrospective study was conducted in patients who visited the National Hospital Organization Nishiniigata Chuo Hospital and National Hospital Organization Nagasaki Medical Center. Among patients diagnosed with JME, those who received LCM as adjunctive therapy for refractory GTCS for at least 2 years from April 2017 to October 2022, and those who achieved seizure freedom or >50% seizure reduction were included. The medical records and neurophysiological data of the patients were retrospectively reviewed.
Results: Four patients met the inclusion criteria. The mean age at onset of epilepsy was 11.3 years (range 10-12), and the mean age at starting LCM was 17.5 years (range 16-21). All patients received two or more antiseizure medications (ASMs) prior to LCM, and five ASMs were administrated in two patients. All patients received valproic acid (VPA) as initial treatment. The number of concomitant ASMs at starting LCM was two in three patients and three in one patient. VPA, levetiracetam (LEV), and clobazam were the most common concomitant ASMs at last visit. Three of four patients had seizure freedom for more than two years, and the one remaining patient had >50% seizure reduction for more than one year. Only one patient had recurrent myoclonic seizures after starting LCM. The mean LCM dose at the last visit was 425 mg/day (range 300-600).
Conclusion: This case series demonstrated the long-term efficacy of LCM adjunctive therapy for patients with uncontrolled GTCS in JME. Adjunctive LCM therapy would be one of the treatment options for JME with drug-resistant GTCS which is not responsive to standard ASMs such as VPA, LEV, and lamotorigine.

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PPAR modulators potential in seizure control and neuronal protection in status epilepticus model in rats compared to antiseizure drugs

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Purpose: Status epilepticus (SE) can lead to epileptogenesis because of resultant neuronal damage. Considering peroxisome proliferator-activated receptor-modulator's (PPAR-m) anti-inflammatory and neuro-modulatory effects, this study investigated their role on seizure control, neurobehaviour, neurodegeneration and neuroinflammation.
Method: This study was performed in two parts: a) dose-finding, and b) acute and long-term effect of drug study in lithium-pilocarpine induced SE model in Wistar rats (200-250g). In optimal dose (OD)-finding study, rats were administered test drugs (PPAR-m) i.e. fenofibrate 50/100/200 mg/kg, pemafibrate 0.5/1.0/1.5 mg/kg, and saroglitazar 1.0/3.0/5.0 mg/kg from day -3 to 3. In second part, rats were randomised into 13 groups (n=06) including normal-control, SE-control, OD of fenofibrate, pemafibrate, and saroglitazar as alone and in combination with valproate and perampanel. SE was induced on day 1 and drugs were administered from -3 to 21 days. Seizure parameters, neurobehavior(elevated-plus-maze, passive-avoidance,

open-field, and novel-object-recognition test), neurodegeneration, total antioxidant capacity (TAC) and neuroinflammation biomarker were evaluated.
Results: OD for fenofibrate, perampanel and saroglitazar were 200, 1.5 and 3 mg/kg, respectively. In comparison to SE-control, drug-treated groups had significantly higher latency ($p<0.001$), reduced number and % of rats with stage-3/4 seizures ($p=0.003$). Seizure control was better in perampanel vs. PPAR-m alone groups ($p<0.001$), and fenofibrate+valproate vs. valproate group ($p<0.001$). Neurobehavioral impairment and neurodegeneration (myelin sheath and axonal damage by electron microscopy) were reduced in drug treated groups than SE-control ($p=0.001$). In immunohistochemistry, hippocampus/cerebral-cortex region, have reduced neuronal loss in fenofibrate+valproate group compared to others ($p=0.031$). TAC, neuron specific enolase & inflammatory-cytokines (TNF-α, IL-1β and TGF-1β) levels had significant difference between SE-control group and all drug-treated groups; however, there was no significant difference between among treated groups.
Conclusion: PPAR-m have shown better seizure control than SE-control, though less than perampanel. Combination of valproate with fenofibrate led to better seizure-protection and less neuronal-loss than valproate alone.

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Efficacy and tolerability of everolimus in focal cortical dysplasia type II: a phase 2, randomized, double-blind, placebo-controlled clinical trial

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Purpose: Everolimus is a promising treatment option for focal cortical dysplasia type II (FCD II); however, there has been no clinical study to date. This trial assessed the efficacy of everolimus in managing FCD II.
Method: In this crossover, phase 2 trial (ClinicalTrials.gov: NCT03198949), patients with pathologically confirmed FCD II were randomly and blindly assigned (1:1) to the everolimus or matching placebo group. After administering the allocated treatment for 12 weeks, patients were crossed over to the alternative treatment for 12 weeks. The initial everolimus dosage was 4.5 mg/m^2/d, and the target everolimus level was 5–15 ng/mL. The primary outcome was a proportion of patients with ≥50% seizure reduction from baseline in the last four weeks of the core phase. Patients who completed the core phases could participate in an open-label 28-week extension phase.
Results: Between May 11, 2017, and June 19, 2020, 21 patients completed the core phases. The primary outcome, ≥50% responder rate did not differ between everolimus and placebo (24% vs. 19%, p = 0.66). However, high response (seizure freedom or ≥90% reduction) was observed in only four patients taking everolimus during the core phase, and the estimated probability of a high response rate was higher with everolimus than with placebo (estimated OR, 3.2; 95% CI, 1.1–9.4; p = 0.036). High response sustained throughout the 28 weeks of the

extension phase.
Conclusion: Everolimus showed potent long-term anti-seizure efficacy in patients with FCD II. Everolimus should be tried for at least 12 weeks as a treatment option for FCD II.

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Compulsive respiratory stereotypies in SYNGAP1 – is Fenfluramine a treatment option?

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Purpose: Case report on efficacy and safety of Fenfluramine (FFA) on compulsive respiratory stereotypies (CRS) in a patient with SYNGAP 1.
CRS are rarely observed in patients with autism spectrum disorder (ASD) and characterized by syncopal attacks triggered by self-induced Valsalva maneuvers. CRS were successfully treated with high-dose Fenfluramine FFA, initially an anti-obesity drug, withdrawn from the market due to its cardiac side effects. FFA is currently used in lower dosage as effective ASM in Dravet patients.
SYNGAP 1 mutations lead to downregulation of total SYNGAP 1 protein with enhancement of synaptic transmission via upregulated RAS-RAF-MEK-ERK pathway and play a major role in ASD, epilepsy and developmental impairment.
Method: We report on a 19 year-old male patient with a pathogenic SYNGAP 1 mutation with mental impairment, refractory epilepsy, severe ASD and repetitive CRS. EEG data with corresponding video sequences of CRS collected before starting FFA within the framework of an individual curative trial. Effects of FFA are evaluated in terms of CRS and seizure reduction, change in behavior and attention according to parents' observations.
Results: Prior to FFA, patient experienced several hundred self-induced CRS daily. Epileptic seizures (arrest, fixed gaze, and eyelid myoclonia) occurred 1-5 times daily accompanied by non-lateralized poly-spike wave complexes. FFA loading was tolerated up to a dose of 0,42 mg/kg/d (27mg) without side effects. Reduction of CRS and seizures by approx. 50% and positive effect on patient alertness, attention and behavior was reported.
Conclusion: Unlike complete control of CRS on FFA in patients with ASD in the literature, our patient showed merely a 50% reduction of CRS and seizures and positive effects on alertness, attention and behavior. While in the original publications FFA doses of up to 60mg/d were used, currently the maximum permissible dose is 27mg/d, which may account for the weaker but still remarkable effect in our patient.

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Antiseizure medication shortages: what is the patients' point of view?

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Purpose: In the last decade switching from brand to generic or between generic antiseizure medications (ASMs) has often been shown to be safe. But with the increasing frequency of ASM shortages new problems arose. In 2011 we performed a study in German speaking countries to explore the patient´s point of view about generic substitution. We decided to repeat this study and extend it to the experience of the patients with delivery problems of ASMs.
Method: In March 2022 a questionnaire was placed on www.epilepsie-online.de, the internet platform from a German patients' organization, which is visited by patients and relatives of other German speaking countries, too. The questionnaire´s issues were personal informations, the experience with delivery problems of ASMs, the opinion about using generics in general and especially in treating epilepsy with ASMs. The internet survey was open until November 2022.
Results: 158 patients with epilepsy or relatives of patients with epilepsy participated.
86 (= 54.4%) of the responders reported delivery problems in a total of 116 cases (i.e. 1.35/responder). The proportion of responders reporting delivery problems differed between the countries significantly (Chi square p <0.004). This was mainly due to the higher amount of delivery problems reported from Germany than from Switzerland (60.4% vs. 24%, Chi square p < 0.001).To 83.7% of the responders the delivery problems were communicated by the pharmacists. In 41.9% the delivery problems were coped by generic substitution. In 44% of these responders breakthrough seizures occurred. To 14%. of responders other doses of the ASM were prescribed. 20.9% of responders looked in other pharmacies for the ASM and 18.6% stocked up their ASMs.
Conclusion: Delivery problems of ASMs are often experienced by people with epilepsy and their relatives in German speaking countries. Coping the problem with generic substitution sometimes results in breakthrough seizures.

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Normalization and first cross sectional validation of an extended adverse event profile (E AEP)

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Purpose: The Liverpool Adverse Event Profile (L AEP) is commonly applied in clinical practice

and in pharmacological trials for the assessment and monitoring of side effects of antiseizure medication (ASM). Normative data would be appreciated to put patients´ complaints into perspective.
Method: An extended 32 question AEP (E AEP) which highly correlates with the L AEP was given to 537 healthy subjects (m/f 167/370) and 1605 patients with epilepsy as part of the Bonn ASM side effect registry. The tool was factor analyzed, standardized in regard to age, gender, and repeated application, and related to drugload and individual substances (with N> 100) on item level and scale level (total E AEP and subscales cognition, dizziness, energy, physiology, aggression, sexuality)
Results: Compared to non-normalized results, on item level between one and two third less problematic responses were noted after normalization. Binary regression analyses reveal differential effects of antiseizure drug treatment but also of antidepressants and neuroleptics on complaint domains. The results reflect both, known drug side effects as well as indications. The explained variance, however, was poor. Patients´ explicit attributions of problems to drugs did hardly improve the correlation of the E AEP and treatment parameters.
Conclusion: Application of a standardized AEP is highly recommended in order not to overestimate treatment related problems in patients with epilepsy. It allows evaluation on item and scale level for individuals and for groups in drug trials. Plausible relations to individual drugs and to drug load can be demonstrated. The explanatory power, however, was low. Drug related complaint patterns reflect known drug side effects (e.g. perampanel and brivaracetam and aggression) as well as drug indications (e.g. lamotrigine for depression), the latter in particular when considerations of side effects have found their way into treatment decisions. Longitudinal evaluation with repeated application along with changes of drug treatment is in progress.

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The impact of perampanel on cardiovascular risk factors in adult patients with focal epilepsy

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Purpose: To determine if perampanel affects the cardiovascular risks in dual therapy in patients with focal epilepsy.
Method: We observed 47 patients with focal epilepsy, aged from 35 to 67 years. Cholesterol and glucose levels and blood pressure were examined during perampanel therapy in dual therapy. Duration of therapy varied from 7 to 18 months.
Results: A total cholesterol level in patients with focal epilepsy before and after 7-18 months of the therapy of perampanel in a dual therapy : PER + CBZ (n=8) 6, 08 ± 0.27 mmol/L vs7.10 ± 1.04 mmol/L (p<0.06), PER + LEV (n=20) 5.43 ± 0.19 vs 5.12 ± 0.11 mmol/L (p >0.05)), PER

+ VPA (n=8) 6.49 ± 0.14 vs 6.26 ± 0.16 mmol/L (p>0.05), PER + LCM (n=11) 5 .91 ± 0.11 vs 5.87 ± 0.12 mmol/l (p>0.05). The glucose level: 5.5 ± 1.9vs 5.8 ± 1.5 mmol/l. The blood pressure: SBP 126.1 ± 1.6 mm Hg vs 123.0 ± 1.3 mm Hg (p>0.05), DBP 81.4 ± 1.2 vs 76.5 ± 1.3 mmHg (p>0.05)

Conclusion: Patients with focal epilepsy in most cases need antiepileptic drugs throughout life. With age the burden of comorbid diseases increases, and cardiovascular diseases are especially important. Hypercholesterolemia, hyperglycemia and high blood pressure are the most dangerous risk factors for fatal disorders such as heart attack and stroke.

According to our study perampanel doesn't affect blood pressure, cholesterol and glucose levels in patients with focal epilepsy taking perampanel in a dual therapy. It was observed that total cholesterol increases in patients taking perampanel in combination with carbamazepine. Perampanel may be the best-choice medication for long-term dual therapy in patients with focal epilepsy and cardiovascular risks because of the possibility to avoid a negative impact of prolonged antiepileptic therapy on risks of fatal cardiovascular comorbidities such as stroke and heart attack.

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Perampanel for treatment of adolescent patients (aged ≥12 to <18 years): real-world evidence from PERMIT 2

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Purpose: To assess the effectiveness and safety/tolerability of perampanel (PER) when used to treat adolescent patients in everyday clinical practice.

Method: A pooled analysis was conducted of data from adolescent patients (aged ≥12 to <18 years) included in PERMIT, a pooled analysis of 44 PER clinical practice studies worldwide, and PROVE, a Phase IV study of PER when used during routine clinical care at US centres (PERMIT 2). Retention was assessed after 3, 6 and 12 months. Effectiveness was assessed by seizure type (focal, generalised) at the last visit (last observation carried forward). Effectiveness assessments included responder rate (≥50% seizure frequency reduction) and seizure freedom rate (no seizures since at least the prior visit). Safety/tolerability was assessed by evaluating adverse events (AEs) and AEs leading to discontinuation.

Results: A total of 559 adolescent patients were included (Full Analysis Set; 50.3% male; mean age, 14.9 years; mean epilepsy duration, 8.8 years). Baseline seizure types were focal only (65.0%), generalised only (30.6%) and both focal and generalised (4.4%). Retention, effectiveness and safety/tolerability were assessed for 547, 299 and 537 patients, respectively. At 3, 6 and 12 months, retention rates were 85.9%, 76.7% and 59.2%, respectively. At last

visit, responder and seizure freedom rates were, respectively, 47.9% and 17.9% for focal seizures, and 68.4% and 40.8% for generalised seizures. AEs were reported for 41.9% patients (most commonly: somnolence [8.6%], irritability [7.4%], dizziness/vertigo [6.0%], aggression [5.0%]). Over 12 months, 16.6% patients discontinued due to AEs. Psychiatric AEs were reported for 22.2% patients; 10.6% of those with psychiatric AEs discontinued (most commonly with: aggression [2.6%], behavioural disorders [2.6%], irritability [2.6%], depression [1.1%]).
Conclusion: PER was effective and generally well tolerated when used to treat adolescent patients (aged ≥12 to <18 years) with focal and generalised seizures under everyday clinical practice conditions.

Supported by Eisai.

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Real-world experience of treating patients aged <12 years with perampanel

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Purpose: Real-world evidence on the use of perampanel (PER) in paediatric patients is limited. This study assessed the effectiveness and safety/tolerability of PER when used in paediatric patients in everyday clinical practice.
Method: A pooled analysis was conducted of data from patients aged <12 years included in PERMIT, a pooled analysis of 44 PER clinical practice studies worldwide, and PROVE, a Phase IV study of PER when used during routine clinical care at US centres (PERMIT 2). Retention was assessed after 3, 6 and 12 months. Effectiveness was assessed by seizure type (focal, generalised) at the last visit (last observation carried forward). Effectiveness assessments included responder (≥50% seizure frequency reduction) and seizure freedom (no seizures since at least the prior visit) rates. Safety/tolerability was assessed by evaluating adverse events (AEs) and AEs leading to discontinuation.
Results: Full Analysis Set included 297 patients aged <12 years (50.0% male; mean age, 7.7 years; mean epilepsy duration, 5.3 years). Baseline seizure types were focal only (60.6%), generalised only (32.6%) and both focal and generalised (6.8%). Retention, effectiveness and safety/tolerability were assessed for 281, 95 and 284 patients, respectively. At 3, 6 and 12 months, retention rates were 80.4%, 69.1% and 52.4%, respectively. At last visit, responder and seizure freedom rates were, respectively, 52.2% and 32.6% for focal seizures, and 50.0% and 17.9% for generalised seizures. AEs were reported for 34.9% of patients (most commonly: aggression [4.9%], behavioural disorders [3.5%], irritability [3.5%]). Over 12 months, 15.0% of patients discontinued due to AEs. Psychiatric AEs were reported for 20.1% of patients;

10.6% of those with psychiatric AEs discontinued (most commonly with: behavioural disorders [2.9%], aggression [1.8%], irritability [1.5%]).
Conclusion: PER was effective and generally well tolerated when used to treat patients aged <12 years with focal and generalised seizures in everyday clinical practice.

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Perampanel for treatment of focal and generalised epilepsy in elderly patients (aged ≥65 years) in clinical practice: evidence from PERMIT 2

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Purpose: Evidence for using perampanel (PER) in elderly patients is limited since such patients are typically excluded from clinical trials. This study assessed the effectiveness and safety/tolerability of PER in elderly patients treated in everyday clinical practice.
Method: A pooled analysis was conducted of data from elderly patients (aged ≥65 years) included in PERMIT, a pooled analysis of 44 PER clinical practice studies worldwide, and PROVE, a Phase IV study of PER when used during routine clinical care at US centres (PERMIT 2). Retention was assessed after 3, 6 and 12 months. Effectiveness was assessed by seizure type (focal, generalised) at the last visit (last observation carried forward). Effectiveness assessments included responder (≥50% seizure frequency reduction) and seizure freedom (no seizures since at least the prior visit) rates. Safety/tolerability was assessed by evaluating adverse events (AEs) and AEs leading to discontinuation.
Results: Full Analysis Set included 394 patients aged ≥65 years (52.0% female; mean age, 72.5 years; mean epilepsy duration, 27.1 years). Baseline seizure types were focal only (90.8%), generalised only (6.5%) and both focal and generalised (2.7%). Retention, effectiveness and safety/tolerability were assessed for 371, 298 and 351 patients, respectively. At 3, 6 and 12 months, retention rates were 87.1%, 77.0% and 60.9%, respectively. At last visit, responder and seizure freedom rates were, respectively, 69.1% and 39.0% for focal seizures, and 70.6% and 52.6% for generalised seizures. AEs were reported for 55.0% patients (most commonly: dizziness/vertigo [16.2%], somnolence [9.7%], irritability [7.4%], instability/ataxia [6.3%]). Over 12 months, 23.9% patients discontinued due to AEs. Psychiatric AEs were reported for 18.9% patients; 9.7% of those with psychiatric AEs discontinued (most commonly with: irritability [3.5%], behavioural disorders [2.1%], depression [1.2%]).
Conclusion: PER was effective and generally well tolerated when used to treat elderly pa-

tients (≥65 years) in everyday clinical practice.

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Perampanel for treatment of Asian patients with focal and generalised epilepsy in clinical practice: evidence from PERMIT 2

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Purpose: To evaluate the effectiveness, safety and tolerability of perampanel (PER) when used to treat Asian patients in everyday clinical practice.
Method: A pooled analysis was conducted of data from Asian patients included in the Perampanel pooled analysis in effectiveness and tolerability (PERMIT) study and the Perampanel Real-world Evidence (PROVE) study (PERMIT 2). PERMIT was a pooled analysis of 44 real-world prospective, retrospective and cross-sectional studies from 17 countries in which patients with focal and generalised epilepsy were treated with PER. PROVE was a Phase IV, retrospective, noninterventional study assessing the retention, dosing, efficacy and safety of PER in epilepsy patients treated in routine clinical care in the US. Retention timepoints included 3, 6 and 12 months. Effectiveness was assessed by seizure type (focal, generalised) at the last visit (last observation carried forward). Effectiveness assessments included responder rate (≥50% seizure frequency reduction) and seizure freedom rate (no seizures since at least the prior visit). Safety/tolerability was assessed by evaluating adverse events (AEs) and AEs leading to discontinuation.
Results: A total of 730 Asian patients were included (47.3% female; mean age 40.1 years): PERMIT included 689 Asian patients and PROVE included 41. Mean time under PER treatment was 9.5 months. Retention rate at 12 months was 51.7%. At the last visit, seizure freedom and responder rates were 32.4% and 62.2%, respectively, for focal-onset seizure only, and 47.1% and 67.3%, respectively, for generalised-onset seizure only. AEs were reported by 47.6% of patients. The most frequently reported AEs were dizziness/vertigo (15.0%), somnolence (6.3%), irritability (6.0%) and apathy (5.0%). AEs led to discontinuation in 22.5% of patients.
Conclusion: PER was effective and generally well tolerated when used to treat Asian patients with focal and generalised seizures in everyday clinical practice.

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Treatment of adult epilepsy patients with Perampanel: evidence from real-world studies

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Purpose: To assess the effectiveness and safety/tolerability of perampanel (PER) when used to treat adult patients in everyday clinical practice.
Method: A pooled analysis was conducted of data from adult patients (aged ≥18 to <65 years) included in PERMIT, a pooled analysis of 44 PER clinical practice studies worldwide, and PROVE, a Phase IV study of PER when used during routine clinical care at US centres (PERMIT 2). Retention was assessed after 3, 6 and 12 months. Effectiveness was assessed by seizure type (focal, generalised) at the last visit (last observation carried forward). Effectiveness assessments included responder rate (≥50% seizure frequency reduction) and seizure freedom rate (no seizures since at least the prior visit). Safety/tolerability was assessed by evaluating adverse events (AEs) and AEs leading to discontinuation.
Results: A total of 5381 adult patients were included (Full Analysis Set; 51.2% female; mean age, 38.1 years; mean epilepsy duration, 23.1 years). Baseline seizure types were focal only (81.6%), generalised only (14.6%) and both focal and generalised (3.8%). Retention, effectiveness and safety/tolerability were assessed for 5125, 3873 and 4943 patients, respectively. At 3, 6 and 12 months, retention rates were 88.7%, 78.4% and 62.4%, respectively. At last visit, responder and seizure freedom rates were, respectively, 44.6% and 14.6% for focal seizures, and 73.5% and 52.0% for generalised seizures. AEs were reported for 50.1% of patients (most commonly: dizziness/vertigo [14.5%], somnolence [8.9%], irritability [7.5%]). Over 12 months, 17.7% of patients discontinued due to AEs. Psychiatric AEs were reported for 21.4% of patients; 10.6% of those with psychiatric AEs discontinued (most commonly with: irritability [3.2%], behavioural disorders [2.2%], mood disturbance [1.7%], aggression [1.1%]).
Conclusion: PER was effective and generally well tolerated when used to treat adult patients (aged ≥18 to <65 years) with focal and generalised seizures in everyday clinical practice.

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Cannabidiol plus everolimus for the treatment of TSC: two cases

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Purpose: Tuberous sclerosis complex (TSC) is a multi-systemic disease caused by pathogenic variants in *TSC1* (9q34) or *TSC2* (16p13.3), encoding for two onco-suppressors, whose loss-of-function leads to the excessive activation of the mTOR pathway. About 90% of TSC patients develop epilepsy and most cases are drug-resistant. The inhibitor of mTOR everolimus (Votubia®) has gained approval for the treatment of refractory seizures in patients with TSC aged above 2 years. Recently, also Epidiolex®, highly purified cannabidiol (CBD), has gained approval for the same indication. Evidence for their combination is low. We report on two TSC patients under combined treatment everolimus+CBD.
Method:
Children with TSC and drug-resistant epilepsy treated with everolimus received adjunctive treatment with CBD at a starting dose of 5 mg/kg/die up to 25 mg/kg/die. The clinical outcome was evaluated as 25-50% (partial responder) or ≥50% (responder) reduction in seizures frequency as compared to the baseline. Tolerability was evaluated recording the adverse events (AE) through anamnestic interview of the caregiver and results of the laboratoristic exames.
Results: Two patients with TSC, mean age 4±1 (±SD) years, and deletion of 18 nucleotides in *TSC2* (c.5238_5255del; p. His1746_Arg1751del) treated with everolimus (mean dose, 3.5 mg/die) received adjunctive treatment with CBD. The mean number of concomitant anti-seizure medications was 3. The baseline seizure frequency was 5/episodes/die and 1 episode/die, respectively. After a mean follow-up of 9±3 months, the mean dose of CBD was 10 mg/kg/die. One patient was a partial responder while the other was a responder. No AE were reported. In one case an increase of the plasma levels of everolimus was observed (14.47 ng/mL), resolved after reducing the posology.
Conclusion: These two cases suggest that the combination everolimus+CBD in TSC is efficient and tolerable. A “start low, go slow” approach designed on the patient is strongly encouraged.

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Prospective long-term seizure free outcomes in subjects with medically resistant focal epilepsy: results from the HEP2 study

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Purpose: Few studies have prospectively determined seizure free outcomes in people with

medically resistant focal epilepsy followed for extended durations. The Human Epilepsy Project 2 (HEP2) is a multicenter observational study that prospectively tracked seizure outcomes for up to 39 months. We now report the seizure free outcomes in our patients.
Method: Subjects met the following qualifications: experienced failure of adequate trials of 4 anti-seizure medicines (ASMs), having ≥2 focal seizures per month for 3 months before enrollment, and receiving ≥1 ASM at baseline. Seizure outcomes and medication changes were determined in 3-month epochs, using data from electronic seizure diaries, monthly study coordinator check-ins, and medical records.
Results: 129 / 146 subjects provided evaluable prospective seizure data of ≥3 months, 119 provided ≥ 6 months, and 99 provided ≥12 months. 17 subjects (13.19%), 10 (7.75%), and 4 (3.10%) had 3-, 6-, or 12-month seizure free epochs, respectively. There were no significant differences in age, biological sex, duration of epilepsy, or number of ASMs or seizure frequency at baseline in subjects with and without seizure free epochs. No significant differences were revealed between those who did and did not experience seizure freedom, with respect to frequency of medication additions, subtractions, or dose changes during the study.
Conclusion: Subjects with medically refractory epilepsy have a small but meaningful opportunity to achieve seizure freedom employing existing therapies. These results should be kept in mind when analyzing long-term results of novel therapies.

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Long-term safety and efficacy of add-on cannabidiol for tuberous sclerosis complex-associated seizures: 3-year results from an open-label extension trial

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Purpose: Add-on cannabidiol (CBD) demonstrated efficacy with an acceptable safety profile in patients with tuberous sclerosis complex (TSC) in a phase 3 randomised controlled trial (RCT). Here, we report safety and efficacy for the full follow-up of the open-label extension (OLE) trial following 156 weeks of treatment.
Method: Patients in the OLE received plant-derived highly purified CBD medicine (Epidyolex®; 100 mg/mL oral solution; GW Pharma [International] B.V.), titrated to 25 mg/kg/day (maximum 50 mg/kg/day). Endpoints included safety, percentage change from RCT baseline in seizure frequency per 28 days, responder rates across 12-week treatment windows and

changes in patients' overall condition on Subject/Caregiver Global Impression of Change (S/CGIC) scale.
Results: Overall, 199 patients entered the OLE, and 34 (17%) completed 156 weeks of treatment; median (range) treatment time during OLE was 631 days (18–1462). Adverse events (AEs) were reported in 96% of patients, serious AEs in 28%, and 9% discontinued treatment due to an AE. Most frequently reported AEs were diarrhoea, seizures, pyrexia, and decreased appetite. Median reduction from baseline in TSC-associated seizures ranged from 53%–90% across 12-week windows through 156 weeks. Reductions in TSC-associated seizures ≥50%, ≥75%, and 100% were maintained up to 156 weeks, ranging from 52%–78%, 29%–69%, and 6%–31%, respectively. Improvement on S/CGIC was reported by 105/118 patients/caregivers (89%) at 52 weeks and 68/73 (93%) at 104 weeks.
Conclusion: Add-on CBD treatment was well tolerated and produced sustained reductions in TSC-associated seizures for up to 156 weeks in patients treated in the OLE, supporting long-term use of CBD for treatment of seizures associated with TSC.

Funding: Jazz Pharmaceuticals, Inc.

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The efficacy and safety of fenfluramine in the treatment of Dravet syndrome and Lennox-Gastaut syndrome: evidence from randomized controlled trials

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Purpose: To evaluate the efficacy, safety, and tolerability of fenfluramine in drug-resistant epilepsy including Dravet syndrome and Lennox-Gastaut syndrome, and provide further evidence for the optimal dosage to guide clinical use.
Method: MEDLINE, Embase, Cochrane Library, and ClinicalTrial.gov were searched for relevant literature published from 1995 to November 1, 2022. Eventually, 3 randomized placebo-controlled trials on DRE (DS and LGS) with 469 patients were included.
Results: We pooled 469 patients from 3 RCTs. The primary outcome was at least 50% reduction in monthly seizure frequency (MSF) and the secondary endpoints were at least 75% reduction, near seizure freedom (seizure frequency ≤1), seizure freedom, as well as investigator- and caregiver/parents-rated clinical global impression improvement scale. It was found that fenfluramine (0.2 mg/kg/d, 0.4 mg/kg/d, 0.7 mg/kg/d) showed significant efficacy over placebo in terms of at least 50% reduction (*RR 2.67, 95%CI[1.59,4.48], P<0.001; RR 11.77, 95%CI[2.95,46.89], P<0.001; RR 3.26, 95%CI[1.96,5.42], P=0.002,* respectively) and at least 75% reduction (*RR 4.36, 95%CI[1.50,12.66], P=0.007; RR 15.35, 95%CI[2.12,111.18], P=0.007; RR 7.41, 95%CI:[1.60,34.33], P=0.01*, respectively) in MSF from baseline. And significantly more patients receiving fenfluramine than placebo were rated as much improved or very much improved by both investigators (*RR 3.52, 95%CI[1.43, 8.64]*) and caregivers/parents (*RR 3.51, 95%CI[2.14, 5.75]*). The most common treatment-emergent adverse events were decreased appetite, diarrhoea, fatigue, and weight loss, with no valvular heart disease (VHD) or

pulmonary hypertension (PAH) observed in all participants.
Conclusion: Low-dose fenfluramine has shown good efficacy, safety, and tolerability in patients with DS and LGS, with no clinical evidence of VHD and PAH. Nevertheless, the long-term efficacy and safety of fenfluramine need to be verified in further studies.

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Adjunctive cenobamate in highly active and ultra-refractory focal epilepsy: A 'real-world' retrospective study

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Purpose: To study cenobamate's efficacy and tolerability in a 'real-world' cohort of patients with ultra-refractory focal epilepsy (≥5 failed epilepsy treatments, including anti-seizure medications [ASM], epilepsy surgery and vagus nerve stimulation [VNS]) and highly-active seizures (>15 seizures per month).
Method: We conducted a single-centre retrospective analysis of consecutive adults treated with cenobamate between October 2020 and September 2022. All patients received cenobamate through an Early Access Program (EAP). Cenobamate retention, seizure outcomes, treatment-emergent adverse events (TEAEs), and adjustments to concomitant ASMs were analysed.
Results: Fifty-seven patients received cenobamate for at least three months (median treatment duration, 11 months). Baseline demographics were consistent with highly active (median seizure frequency= 60/month) and ultra-refractory focal epilepsy (median previously failed ASMs= nine). Most (87.8%) had prior epilepsy surgery and/or VNS. Fifty patients (87.7%) remained on cenobamate through September 2022. Five patients stopped cenobamate due to lack of efficacy, and one patient stopped due to TEAEs. One patient died from factors unrelated to cenobamate. Among patients who continued cenobamate, three achieved seizure freedom (5.3% of cohort), 23 had a 75-99% reduction in seizures (41.1% of cohort), and 16 had a 50-74% reduction (28.6% of cohort). In these patients who continued cenobamate, the median dose was 250mg/day (IQR 100mg, range 75-350mg/day). Cenobamate led to the abolition of focal to bilateral tonic-clonic seizures (FBTCS) in 55.6% (20/36) of patients with active convulsions at baseline. Three-quarters of patients reported at least one TEAE, most commonly fatigue and somnolence. TEAEs were relatively manageable by reducing the overall ASM burden, most often clobazam, eslicarbazepine and perampanel.
Conclusion: Patients with highly active and ultra-refractory focal epilepsy experienced meaningful seizure outcomes on cenobamate, with a particularly robust reduction in FBTCS. Cenobamate was generally well tolerated if accompanying ASMs were reduced or stopped, particularly clobazam and sodium channel blockers.

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Long-term treatment effects of soticlestat in patients with Dravet syndrome or Lennox–Gastaut syndrome: interim data from the ENDYMION 1 trial

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Purpose: Soticlestat, a cholesterol 24-hydroxylase selective inhibitor, was well tolerated and reduced seizure frequency in children with Dravet syndrome (DS) or Lennox–Gastaut syndrome (LGS) over 12 weeks in the phase 2 ELEKTRA study. ENDYMION 1 aims to evaluate the long-term safety, tolerability and efficacy of soticlestat in patients with developmental and epileptic encephalopathies (DEEs), including DS or LGS.
Method: ENDYMION 1 (NCT03635073) is an ongoing, phase 2, open-label extension study of adjunctive soticlestat (≤300 mg twice daily, weight-adjusted in children) enrolling adults with DEEs and children with DS or LGS who completed a phase 1b/2a study (NCT03166215) or ELEKTRA (NCT03650452), respectively, or received ≥10 weeks of treatment. Patients undergo dose optimization followed by a maintenance period. Those discontinuing treatment undergo a 4-week safety follow-up period that includes tapering. Primary endpoints include incidence of treatment-emergent adverse events (TEAEs); secondary endpoints include change in seizure frequency from baseline.
Results: At the time of analysis, 47 patients with DS and 83 patients with LGS were enrolled, with median (range) soticlestat exposures of 80.1 (1.4–134.0) weeks and 88.3 (1.0–178.0) weeks, respectively. For DS and LGS, respectively: 41 (87.2%) and 72 (86.7%) patients experienced TEAEs; 21 (44.7%) and 36 (43.4%) patients experienced one or more drug-related TEAEs, which were serious in 1 (2.1%) and 5 (6.0%) patients; and 3 (6.4%) and 10 (12.0%) discontinued soticlestat owing to drug-related TEAEs. At weeks 1–12, 49–60, and 97–108, respectively, median changes in seizure frequency from baseline of ELEKTRA were –28.0% (n=46), –59.6% (n=28), and –53.4% (n=22) in patients with DS and –28.4% (n=79), –17.7% (n=49), and –27.7% (n=35) in patients with LGS.
Conclusion: This interim analysis of ENDYMION 1 showed no new safety signals and a sustained seizure reduction in those receiving soticlestat.

Study funded by Takeda Pharmaceutical Company Limited.

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Building on the European reference networks to shape research on rare and complex epilepsies

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Purpose: Present the experience of the cross-borders European Reference Network (ERN) for rare and complex epilepsies (EpiCARE: https://epi-care.eu/) to promote and support clinical research activities. The ERNs are funded by the European Commission to support joint efforts of medical experts and patient advocates, for better care and promotion of collaborative research.
Method: EpiCARE created a Research Council (RC) to coordinate and support research activities initiated by one or more of the 50 EU-based medical teams composing the network. They involve more than 500 neurologists and child neurologists with expertise in epilepsy care and research, working in collaboration with other centres in Europe and internationally.
Results: EpiCARE Research Council missions are, between others, quality control of grant requests; strategic coordination; input on methodological issues; selection of young researchers for presentations at congresses; liaison with patient groups; other. EpiCARE supported the creation, within Epilepsy Alliance Europe, of a European Consortium for Epilepsy Trials (ECET), providing expertise for the design and feasibility of drug trials. An in-development central registry will be a powerful enabler of research and trial recruitment. A dedicated genetic platform facilitates recruitment for cohorts of patients carrying rare variants in genes.
Conclusion: With the support of the RC, EpiCARE members submitted 4 EJP-RD calls (one accepted), 5 HORIZON calls (two accepted in first phase), one COST ACTION application is ongoing, and 2 projects are being developed for a new EJPRD call. The genetic platform diffused 11 calls and collaborations have been instituted. Together with the ILAE, the European Academy of Neurology, the European Paediatric Neurology Society and other ERNs for neurological disorders the EpiCARE RC encourages expert medical teams to shape the future of research within the WHO "Intersectoral Global Action Plan on Epilepsy and other neurological disorders".

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Co-medication management: key to optimize the efficacy and tolerability of Cenobamate

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Purpose: In this study we provide our experience as a refractory epilepsy unit in a real-world practice on optimizing CNB efficacy and minimizing adverse effects by rapidly reducing co-medications.
Method: We performed a prospective observational study of patients with focal DRE treated with CNB in our clinic.
Results: A total of 34 patients were included. Twenty-one patients had reached 12 months of follow-up by December 2022. Mean CNB dose (mg) was 207.8 (SD 25.7), 267.2 (SD 53.9) and 326.2 (SD 80) at 3, 6 and 12 months of follow-up, respectively. Seven patients discontinued treatment (6 due to inefficacy and 1 due to ataxia).
Median seizure reduction was 93.3% at 6 months and 88.9% at 12 months of follow-up. Response rate (≥50% seizure reduction) was 85.7% at 12 months. Responder rate ≥90% was achieved by 10 patients (47.6%) at 12 months. Seven patients (33.3%) were seizure-free at 12 months. PGI-I, including discontinued patients, was very much better/much better in 14 patients (41.2%), a little better in 8 patients (23.5%), no change in 6 patients (17.6%) and much worse/very much worse in 6 patients (17.6%) of patients.
The total defined daily dose (DDD) of co-administered anti-seizure drugs decreased significantly during follow-up (mean 3.6 DDD, SD 1.3 at baseline; mean 1.4 DDD, SD 1.2 at 12 months of follow-up; p<0001). Adverse effects were frequent initially (35.3% ataxia, 52.9% dizziness and 64.7% drowsiness) but were drastically reduced at 12 months (3.8% ataxia, no dizziness and 33.3% drowsiness at 12 months). No skin rash was detected.
Conclusion: We report an outstandingly high seizure frequency reduction and seizure freedom rates when using CNB in highly refractory patients while at the same time reducing co-medication more than half its initial dose. We suggest rapid co-medication reduction might be the approach needed to optimize efficacy and minimize AEs when using CNB.

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Cutaneous reaction to treatment with carbamazepine or DRESS syndrome, description of the first case in Northwestern Colombia

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Purpose: DRESS syndrome is a severe and idiosyncratic drug hypersensitivity reaction characterized by rash, fever, lymphadenopathy, hematologic abnormalities, and multi-organ involvement. The heterogeneity of the clinical manifestation represents a diagnostic challenge for the clinician, requiring a high index of suspicion and ruling out a wide spectrum of differential diagnoses.
Method: We describe the clinical picture and treatment of a 35-year-old patient with epilepsy who was hospitalized for generalized morbilliform lesions concomitant with fever, lymphade-

nopathy, splenomegaly, and eosinophilia. Rule out infectious, autoimmune and neoplastic processes was possible with complementary studies; the history of recent carbamazepine ingestion and the clinical and laboratory data allowed the definitive diagnosis of DRESS syndrome to be established.
Results: The patient received topical and systemic corticosteroids, the clinical manifestations reverted after the second week of hospitalization. The importance of identifying risk factors associated with the appearance of this syndrome is mandatory.
Conclusion: There is no specific treatment for carbamazepine hypersensitivity, measures include drug cessation, skin care, and fluid and electrolyte maintenance, controversy regarding corticosteroid administration continues, probably beneficial in DRESS syndrome induced by carbamazepine; systemic corticosteroids are associated with major complications

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Study 512 Design: Perampanel as first adjunctive therapy in patients aged ≥12 years with focal-onset seizures or generalised tonic-clonic seizures associated with genetic generalised epilepsy

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Purpose: Patients with uncontrolled seizures while on anti-seizure medication (ASM) monotherapy may require adjunctive therapy. Study 512 (NCT04252846) is a prospective, observational, multicentre study to assess the dosage, effectiveness and safety of perampanel as adjunctive therapy in patients aged ≥12 years with focal onset seizures (FOS) and/or generalised tonic-clonic seizures (GTCS) associated with genetic generalised epilepsy (GGE) in clinical care in Europe. Here, we present the design and interim results of Study 512.
Method: Patients received perampanel as the first adjunctive therapy to ASM monotherapy per the investigator's decision. Key inclusion criteria include age ≥12 years, epilepsy diagnosis (FOS, with/without focal to bilateral tonic-clonic seizures, or GTCS associated with GGE), previously treated with ≤2 ASM monotherapies and available baseline seizure frequency data. Key exclusion criteria include episode(s) of status epilepticus ≤6 months pre-screening, ≥2

ASMs in combination (except for cross-titration between ASM monotherapies) and previous/current perampanel use. Patients will be assessed at baseline and as per routine clinical care, with study visits occurring at Months 6 and 12. Endpoints include retention rate, change in seizure frequency, responder/seizure-freedom/seizure-worsening rates, dosing patterns, treatment duration and safety. Descriptive statistics will be used for analysis.
Results: The study was initiated on 20 July 2020, and recruitment terminated on 23 December 2021; 196 patients were enrolled at 45 study sites across ≥5 countries. The mean (standard deviation) age of patients was 39.6 (19.6) years; most common seizure type was FOS (n=151/194; 77.8%). Nearly all patients (n=186/188; 98.9%) were receiving one ASM at baseline, most commonly levetiracetam (n=82/191; 42.9%). Interim study results will be presented in the poster.
Conclusion: Study 512 will provide prospective, observational data on realworld use of perampanel as first adjunctive therapy in patients aged ≥12 years with epilepsy.

Funding: Eisai Inc.; Eisai Ltd.; Eisai Co., Ltd.

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A single centre retrospective review of pharmaceutical grade cannabidiol (epidyolex) treatment in an adult cohort with complex epilepsy

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Purpose: Pharmaceutical grade cannabidiol (epidyolex) is a recently approved antiseizure medication for the treatment of refractory seizures in Lennox-Gastaut Syndrome (LGS), Dravet Syndrome (DS) and Tuberous Sclerosis Complex (TSC). We examined the efficacy, safety, and tolerability of epidyolex from an adult tertiary epilepsy centre.
Method: We conducted a single-centre retrospective analysis of consecutive patients with LGS, DS, and TSC treated with epidyolex between September 2020 and December 2022. Baseline clinical data were obtained from our epilepsy electronic patient record and paper-based medical notes. We analysed seizure outcomes, side effects, and adjustments to concomitant anti- seizure medications (ASMs).
Results: Seventeen patients (53% female) were treated with epidyolex for an average of 7 months (range 2-16 months). Mean age was 32.9 years (range 20-62 years). Mean epilepsy onset was 3.3 years. 82.3% of patients had a diagnosis of LGS, 5.9% had DS, and 11.8% had TSC. Twelve patients had genetic testing, and 50% showed pathogenic mutations. The median of previously failed ASMs was 8 (range 3-17). The median of concomitant ASMs was 4 (range 1-6). Baseline monthly median seizure frequency was 75. Sixteen patients (94.1%) continued epidyolex by January 2023. One patient discontinued due to the lack of efficacy and side effects (ongoing diarrhoea) while uptitrating epidyolex. Overall patients experienced a seizure reduction of 58% on treatment compared to pre-treatment baseline. Seizure reduction was

observed across all three different epilepsy syndromes. Main adverse effects included diarrhoea, skin hyperpigmentation, weight loss, and derangements on liver function test (mainly gamma-glutamyl transferase) which did not require drug discontinuation. In 30% of patients, it was possible to reduce concomitant ASMs by 1.8 per patient (range 1-3).
Conclusion: Our study, in a complex adult cohort, shows that our initial experience prescribing epidyolex is effective in reducing seizures in patients with LGS, DS, and TSC.

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OV329, a next-generation GABA-AT inhibitor, suppresses HPDs following repeat dosing in a mouse model of mesial temporal lobe epilepsy at a dose without ocular toxicity

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Purpose: GABA is the major inhibitory neurotransmitter in the adult CNS and is primarily catabolized by GABA-amino transferase (GABA-AT). Compared to vigabatrin (VGB), the only FDA-approved GABA-AT inhibitor to date, OV329 is highly potent and holds the potential to be the best in-class drug with efficacy at doses without negative retinal effects observed with VGB. Here, we aim to test the efficacy of OV329 in a mouse model of mesial temporal lobe epilepsy (MTLE) and evaluate its ocular safety profile in rats.
Method: MTLE was induced by injecting kainate into the dorsal hippocampus and hippocampal paroxysmal discharges (HPDs) were monitored by EEGs. Four weeks after injury, OV329 (0.3, 1.0, or 3.0 mg/kg/day) or vehicle was administered for 8 days followed by a ~2-week washout period. HPD numbers and duration were evaluated on Days 1, 4, 8, 15 and 23. For ocular safety assessments, albino rats were treated with either vehicle, OV329 (3.0, 10, and 30) or VGB (300 mg/kg/day). In-life ocular examinations (electroretinogram, optical coherence tomography, slit-lamp) were carried out at baseline and on days 10, 20, 31, and 45. Terminal histologic and microscopic analysis was performed on retinal tissue collected on Day 20 or 45.
Results: Once daily dosing of 3 mg/kg OV329 for 8 days significantly reduced the number of HPDs (70 ± 9% at day 8; $p < 0.05$) compared to the baseline in the MTLE model. Daily treatment of OV329 (3.0 mg/kg) for 45 consecutive days in rats did not display negative functional or histological changes in retina as observed with VGB treatment.
Conclusion: These findings demonstrate low, repeat administration of OV329 (3.0 mg/kg) can achieve efficacy in the MTLE seizure model without inducing ocular damage and present an opportunity for a safer GABA-AT inhibitor for the treatment of seizure disorders.

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Outcomes by seizure type from a mirroring clinical practice study of perampanel in 482

adults and adolescents (AMPA)

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Purpose: The AMPA Study (NCT04257604; Study 501) was a prospective, observational, 12-month study to evaluate the efficacy and safety of adjunctive perampanel in patients with focal-onset seizures (FOS), with/without focal to bilateral tonic-clonic seizures (FBTCS), in routine clinical practice in Italy. Here, we report a post hoc analysis of clinical outcomes, particularly treatment-emergent adverse events (TEAEs), by seizure type.
Method: Patients aged ≥12 years with insufficiently controlled FOS, with/without FBTCS, receiving 1–3 anti-seizure medications were prescribed adjunctive perampanel per the approved indication. The primary endpoint was median percent reduction from baseline in seizure frequency/28 days at Month 6. Safety endpoints included monitoring of TEAEs up to 12 months.
Results: Of the 234 patients who received adjunctive perampanel (Safety Analysis Set [SAS]), 202 patients had baseline/post-baseline seizure data and formed the Intent-to-Treat (ITT) Analysis Set. The median percent reduction in seizure frequency/28 days from baseline at Month 6 was 68.3% vs 49.5% in patients with and without FBTCS, respectively (ITT); reduction in FBTCS frequency was 100.0% in patients with FOS and FBTCS at baseline. The incidence of TEAEs and treatment-related TEAEs, as well as TEAE severity (mild, moderate or severe), was comparable between patients with/without FBTCS (SAS). Serious TEAEs were reported in 5.6% and 6.3% of patients with and without FBTCS, respectively; no deaths occurred in either group. TEAEs leading to perampanel dose adjustment were reported by 35.6% and 38.9% of patients with and without FBTCS, respectively. The most common TEAE was dizziness/vertigo (24.4% vs 20.1% for patients with and without FBTCS, respectively).
Conclusion: These data suggest that adjunctive perampanel was efficacious and generally well tolerated in patients with FOS, with/without FBTCS, in a real-world setting; incidences of TEAEs were comparable between patients with/without FBTCS, and no unexpected safety signals emerged.

Funding: The AMPA Study was funded by Eisai S.r.l.

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PERPRISE (PERampanel in patients with PRImary or SEcondarily generalised seizures): first interim analysis of the observational study assessing perampanel as the only adjunctive therapy

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Purpose: Prospective data from Germany mainly reflect perampanel use as late-line adjunctive therapy in complex drug regimens for refractory epilepsies. In this interim analysis of PERPRISE (Study 509; NCT04202159), we evaluate perampanel efficacy as the only adjunctive treatment in clinical practice in Germany.
Method: PERPRISE is a multicentre, prospective, observational, non-interventional study. Patients (≥18 years) with focal to bilateral tonic-clonic seizures (FBTCS) or generalised tonic-clonic seizures (GTCS) due to focal epilepsy or idiopathic generalised epilepsy with ≥1 FBTCS or GTCS within 3 months prior to inclusion are eligible. Perampanel is administered as the only adjunctive treatment to anti-seizure medication (ASM) monotherapy or as a substitute for one ASM during dual therapy. Endpoints include 6- and 12-month retention rate, seizure freedom and safety. The Interim Analysis Set (IAS) comprises the first 100 patients to receive ≥1 dose of perampanel and attend or discontinue prior to the 6-month visit.
Results: As of 25 November 2021, the IAS included n=43, adjunctive; n=55, substitution; and n=2, missing. The most common concomitant ASM was lamotrigine (35.0% [32.6%, adjunctive; 38.2%, substitution]). The mean (standard deviation) last perampanel doses were 4.6 (1.8, adjunctive) and 6.3 (2.5, substitution) mg/day. The 6-month retention rate was 78.0% overall, and 83.7% (adjunctive) and 72.7% (substitution) when stratified by group. Seizure-freedom rates were 58.8% for FBTCS/GTCS (72.2%, adjunctive; 47.9%, substitution) and varied with number of previous ASMs. The incidences of treatment-emergent adverse events (TEAEs) and serious TEAEs were 48.0% and 7.0%, respectively; TEAEs led to perampanel withdrawal in 16.0% of patients. The most common TEAEs were dizziness (9.0%), irritability (7.0%), fatigue (7.0%) and gait disturbance (5.0%).
Conclusion: This interim analysis of perampanel as the only adjunctive treatment for patients with FBTCS/GTCS demonstrated retention rates of >70% after 6 months and high degrees of seizure freedom.

Funding: PERPRISE was funded by Eisai GmbH.

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ELEVATE Study 410: analysis of time to first seizure with perampanel as monotherapy or first adjunctive therapy in patients with focal-onset seizures or generalised tonic-clonic seizures

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Purpose: To present a post hoc analysis evaluating the efficacy of perampanel for focal-onset seizures (FOS) and generalised tonic-clonic seizures (GTCS) assessing time to first seizure following perampanel administration using data from ELEVATE (Study 410; NCT03288129).
Method: ELEVATE was a multicentre, open-label, Phase IV study of perampanel monother-

apy/first adjunctive therapy in patients aged ≥4 years with FOS, with/without focal to bilateral tonic-clonic seizures (FBTCS), or GTCS including Titration (≤13 weeks), Maintenance (39 weeks) and Follow-up (4 weeks) Periods. Patients received perampanel at 2 mg/day, up-titrated after >2 weeks to 4 mg/day (further increases of 2 mg/>2 weeks based on response and tolerability; maximum, 12 mg/day). Endpoints included 3, 6, 9 and 12-month retention rate, seizure freedom, median percent reduction in seizure frequency per 28 days, 50% and 75% responder rates, treatment-emergent adverse events (TEAEs), serious adverse events and treatment discontinuation due to TEAEs. Time to first seizure was assessed in the Full Analysis Set (FAS) using Kaplan–Meier analysis.
Results: The Safety Analysis Set included 54 patients; 40.7% discontinued due mostly to TEAEs (n=10) and lost to follow-up/patient choice (n=3, each). During the Maintenance Period, mean (standard deviation) perampanel dose was 6.4 (2.1) mg/day. The FAS included 52 patients (FOS, n=37 [FOS+FBTCS, n=9]; GTCS, n=11 [FOS+GTCS, n=4]). Median (range) baseline seizure frequency was 2.0 (0.7–105.0); median seizure frequency reductions for FOS and GTCS were 76.1% and 100.0%, respectively. 36.5% of patients discontinued/completed the study without seizures (n=9 in study for >1 year; n=10 discontinued by 9 months). 63.5% of patients experienced seizure(s) with a median (range) time to first seizure of 94 (23, 281) days. Incidences of TEAEs/serious TEAEs were 88.9% and 7.4%, respectively.
Conclusion: Median time to first seizure/seizure frequency reduction findings support the safety and sustained efficacy of perampanel as monotherapy/first adjunctive therapy.

Funding: Eisai Inc.

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Evaluation of OV329, a next-generation GABA-AT inhibitor in a series of pharmacoresistant seizure models through the ninds epilepsy therapy screening program

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Purpose: Reductions of GABA-mediated inhibitory signaling have been associated with seizures and epilepsy. GABAergic neurotransmission can be elevated by inhibition of GABA-amino transferase (GABA-AT), the primary catabolic enzyme of GABA. OV329, a highly potent and specific GABA-AT inhibitor holds the potential to be a next-generation GABA-AT inhibitor. OV329 was enrolled in the NIH/NINDS Epilepsy Therapy Screening Program (ETSP) to examine efficacy in pharmaco-resistant epilepsy models.
Method: Testing was conducted in four standardized epilepsy models: 6 Hz electrical stimulation, maximal electroshock seizures (MES), corneal kindling model (CKM), and intrahippocampal kainate (IHK) injury. Mice were treated with OV329 at a range of doses (1–70 mg/kg PO) and assessed for seizure control at various timepoints. Tolerability and motor impairment was assessed using the Rotarod test.

Results: OV329 was not active in the 6 Hz or MES models. In the CKM, ED_{50} was found to be between 27.9 and 46.7 mg/kg. OV329-treated CKM mice were significantly less likely to reestablish the kindled state at any point following a 55-day washout. Compared to control (100%), kindling status was either delayed or absent in mice treated with OV329 (12.5% and 40% recovered fully kindled status after 40 and 50 mg/kg OV329, respectively). Hippocampal paroxysmal discharges were completely abolished in all IHK mice treated with a single, 30 mg/kg dose, while sedation was noted in 25% of these animals after 8-hours. No motor impairment on the Rotarod test was seen in mice with doses less than 30 mg/kg.
Conclusion: OV329 demonstrated efficacy in the subacute models of epileptogenesis (CKM and IHK) but not in the acute models (6 Hz and MES). A single, high dose of OV329 produced near complete protection from seizure activity in CKM. Future studies are warranted to assess effective dosing strategies based on the pharmacokinetic and pharmacodynamic properties of OV329.

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Towards responsible clinical n-of-1 strategies for rare diseases

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Purpose: N-of-1 strategies can provide high-quality evidence on treatment efficacy at the individual level, and optimise evidence-based selection of off-label treatments for patients with rare diseases. Due to their design characteristics, n-of-1 strategies are considered to lay at the intersection between medical research and clinical care. Therefore, whether n-of-1 strategies should be governed by research or care regulations remains a debated issue. The purpose of this presentation is to discuss criteria to distinguish optimised clinical n-of-1 strategies from research n-of-1 strategies, and correspondingly the ethical and regulatory implications of both approaches.
Method: We reviewed the literature to establish key topics of debate regarding n-of-1 strategies and other optimized care strategies, and review underpinnings and regulations of scientific research, including the Belmont Report of 1979 and the European Clinical Trial Regulation 536/2014. We defined characteristics of research n-of-1 strategies and clinical n-of-1 strategies and delineated the criteria for responsible clinical n-of-1 strategies.
Results: Key differences between scientific research and clinical care involve the aim to obtain

new generalisable knowledge and the burden incurred on individuals by procedures or rules of behaviour applied. N-of-1 strategies tend to be considered research due to the use of a predefined protocol, randomisation, and when the objective is to generate novel knowledge. We argue that clinical n-of-1 strategies aimed solely at improving clinical management of a patient, need not to be subject to the regulations of research. We set standards for responsible optimised clinical n-of-1 strategies with (off-label) treatments for rare diseases, including evaluation of potential risks and benefits of treatments and methodology by an independent multidisciplinary expert panel.
Conclusion: Implementing clinical n-of-1 strategies, as defined here, could help improve clinical management and treatment selection, particularly for populations in which high-quality evidence is lacking, such as rare epilepsies.

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Activation of KCC2 suppresses benzodiazepine refractory status epilepticus and limits the subsequent neuronal injury

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Purpose: Fast synaptic inhibition in the adult brain is mediated by γ-aminobutyric acid type A receptors ($GABA_AR$s), that mediate Cl- dependent neuronal hyperpolarization. Hyperpolarizing $GABA_AR$ currents are critically dependent upon efficient Cl^- extrusion, a process that is facilitated by the neuronal specific $K+/Cl^-$ co-transporter (KCC2). Proper activity of KCC2 is critical for the anticonvulsant efficacy of benzodiazepines (BDZ), which allosterically potentiate $GABA_AR$s . Compromised KCC2 activity is implicated in the pathophysiology of status epilepticus (SE), a medical emergency that rapidly becomes refractory to BDZ (BDZ-RSE). Here we aim to test the efficacy of a KCC2 activator, OV350, in preventing SE in a Kainic acid (KA) induced mouse model of BDZ-RSE and neuronal injuries associated with it.
Method: Using high-throughput screening, we have identified a family of small molecules that directly bind to and activate KCC2. Subsequent optimization for potency and brain exposure resulted in identification of OV350. By using a combination of biochemical, pharmacological, and imaging techniques and EEG recordings, we examined the efficacy of OV350 in KA-induced BDZ-RSE model.
Results: OV350 binds with high affinity to KCC2 and increases its activity, without modifying its stability on the plasma membrane or the phosphorylation of key regulatory residues. KCC2 activation reduces neuronal Cl^- accumulation and limits the development of hyperexcitability. OV350 rapidly accumulates in the rodent brain and does not induce any overt effects on behavior, but selectively elevates EEG gamma power. This compound slowed the development of SE induced by kainate and prevented the subsequent development of BDZ resistance. Moreover, OV350 restored the efficacy of BDZs to terminate ongoing SE and abolished KA-in-

duced neuronal cell death in 48-72 hours following this trauma.
Conclusion: Our results provided evidence that an agent like OV350 that directly enhances KCC2 activity is efficacious in animal models in alleviating BDZ-resistant seizures and limits the subsequent neuronal injury.

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Human Epilepsy Project 2 (HEP2): lifetime and current ASM profile for patients with refractory epilepsy

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Purpose: The Human Epilepsy Project 2 (HEP2) was a prospective, observational multicenter US study focused on identifying clinical characteristics and biomarkers predictive of disease outcome, progression, and treatment response in participants with treatment-resistant focal epilepsy. Here, we report on lifetime and current ASM profiles to determine US treatment patterns.
Method: All subjects had focal epilepsy, at enrollment were 16-65 years old, had failed ≥ 4 ASMs (with at least 2 due to failure of seizure control), and were receiving at least 1 ASM. Subjects were recruited from 10 US epilepsy centers starting 7/31/2018 and were followed for 18-36 months. We analyzed lifetime ASM (taken in past and currently) and current ASM data provided by 146 actively enrolled participants at baseline.
Results: Participant average age at enrollment was 39.7 yo, SD ± 12, and at epilepsy diagnosis was 19.6 yo, SD ± 13.6. 84/146(57.5%) were female, 62/146(42.5%) male. Average lifetime ASM use was 8 ± 4 ASMs. Lifetime ASM use in order of frequency was: Levetiracetam: 135(92.5%), Lamotrigine: 108(74.0%), Lacosamide: 98(67.1%), Carbamazepine: 82(56.2%), Topiramate 73(50.0%), Clobazam 73(50.0%), Zonisamide 71(48.6%), Oxcarbazepine 70(47.9%), Phenytoin 65(44.5%), Phenobarbital 39(26.7%), Brivaracetam 25(17.1%), Eslicarbazepine 22(15.1%). Current/Lifetime (% retaining) use of ASMs, in order, was: Eslicarbazepine 14/22(63.6%), Brivaracetam 15/25(60%), Clobazam 42/73(57.5%), Lacosamide: 53/98(54.1%), Lamotrigine: 47/108(43.5%), Levetiracetam 52/135(38.5%), Zonisamide 27/71(38.0%), Oxcarbazepine 22/70(31.4%), Carbamazepine: 22/82(26.8%), Topiramate 15/73(20.5%), Phenobarbital 5/39(12.8%), Phenytoin 7/65(10.8%).
Conclusion: Levetiracetam demonstrated by far the highest lifetime use (92.5% of subjects vs Lamotrigine, the next highest, at 74.0%). Phenytoin demonstrated the lowest rate of continuation at 10.8%. Eslicarbazepine and brivaracetam had low frequency of use with high retention that might be explained by recent market introduction (less time for drug failure). Lacosamide and lamotrigine had relatively high use and high retention, suggesting a good clinical effectiveness.

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Antiseizure medication exposure in pregnancy - correlation between prescription fill for antiseizure medication and therapeutic drug concentrations in pregnancy

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Purpose: Research into children with prenatal antiseizure medication exposure often rely on information from patient interviews or registers of reimbursed prescriptions to assess exposure status, but more precise estimates of actual exposure levels, e.g., from blood concentration measurements, are lacking. In this study we correlate information from a prescription register with information from drug monitoring during pregnancy.
Method: Pregnant mothers were identified from the Danish Medical Birth Register (1995-2015), and information was retrieved from the Danish National Prescription Registry and the Register of Laboratory Results for Research. We identified women who filled prescriptions for antiseizure medication from 30 days before the first day of the last menstrual period to birth. From the Register of Laboratory Results, we identified serum concentrations measurements in the same women in pregnancy. Results were rounded off to the nearest 10 for confidentiality of study participants.
Results: We identified a total of 241,000 births. Among these pregnancies there were 1,730 births where the mother filled prescriptions for antiseizure medication. The most widely used antiseizure medications among pregnant women were lamotrigine (n = 1,010) and levetiracetam (n = 230). We were able to retrieve drug concentrations in mothers of 460 births. The most widely reported concentration measurements were lamotrigine (n = 300) and levetiracetam (n = 120). Among women who filled Lamotrigine prescriptions in pregnancy, 28% also had a serum concentration measurement in the Register of Laboratory Results during pregnancy. Among women who filled Levetiracetam prescriptions in pregnancy, 53% also had a serum concentration measurement during pregnancy.
Conclusion: A substantial number of pregnant women who fill prescriptions for antiseizure medication in Denmark, also have measurements of antiseizure medication concentrations, which offers a unique opportunity to improve assessment of drug exposure in pregnancy and thereby any associated risks.

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MicroRNA-335-5p suppresses voltage-gated sodium channel expression and may be a target for seizure control

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Purpose: Sodium channel blockers are among the most effective anti-seizure medicines (ASMs) but there remains an urgent need for new therapies for drug-resistant epilepsy (DRE). MicroRNAs (miRNA) are small non-coding RNAs which negatively regulate gene networks by binding to target mRNAs. Several miRNAs control neuronal excitability and, when targeted, can protect against seizures in preclinical models.
Here, we undertook genome-wide miRNA screening of hippocampal tissue from a rat epilepsy model, mice treated with the novel ASM cannabidiol and plasma from DRE patients, and identified convergence on a single target, miR-335-5p. Using different *in vivo* and *ex vivo* techniques, we identified targets of miR-335-5p and show manipulation of miR-335-5p can alter sodium channel function, neuronal network physiology and seizures.
Method: We used published and new small RNA sequencing data, *in silico* target prediction, *ex vivo* brain slice and *in vitro* electrophysiology, and RT-qPCR to probe the molecular and biophysical impacts of miR-335-5p manipulation. *In vivo* studies were performed in adult C57/BL6 mice using intracerebroventricular injections of an antimiR (Ant-335) and intrahippocampal injection of an AAV9 to overexpress miR-335-5p (AVV9-miR-335). Seizures were evoked by pentylenetetrazole (PTZ).
Results: Pathway analysis on predicted and validated miR-335-5p targets identified multiple voltage-gated sodium channels (VGSCs). Inhibition of miR-335-5p resulted in upregulation of several VGSCs in the mouse brain, an increased action potential rising phase and greater excitability of hippocampal pyramidal neurons in brain slice recordings. Blocking of miR-335-5p also increased voltage-gated sodium currents in human iPSC-derived neurons. MiR-335-5p inhibition increased susceptibility to tonic-clonic seizures in the PTZ model, whereas overexpression of miR-335-5p reduced seizure severity and improved survival.
Conclusion: These studies suggest miR-335-5p controls a set of VGSCs and has important effects on brain excitability and seizures. Changes to miR-335-5p may reflect compensatory mechanisms to control excitability and could provide new biomarker therapeutic strategies for different types of DRE.

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Fenofibrate as adjuvant therapy in persons with active epilepsy: a double-blind, randomized, placebo - controlled study

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Purpose: Neuroinflammation, a key pathological feature, persists after the onset of epilepsy and is linked to gradual increase in seizure frequency and duration, and possibly therapeutic resistance. Fenofibrate has shown to have anticonvulsant, anti-inflammatory, antioxidant, and neuroprotective properties in addition to its lipid-lowering effect. In this double-blind, randomized, placebo - controlled study (Clinical trial registry-India number CTRI/2021/03/032317), adjuvant effects of fenofibrate therapy in persons with epilepsy (PWE) were assessed.
Method: Adult PWE were randomly assigned to either fenofibrate or placebo group. For six months, PWE who were receiving ≥2 antiseizure drugs (ASDs) were given 145 mg of fenofibrate/placebo, in addition to ongoing ASDs. At baseline and after six months, changes in seizure frequency, drug responder rate, total antioxidant capacity (TAC), neurotrophin-3 and quality of life were evaluated. Safety-parameters i.e., hematological/biochemical, muscular strength, body composition and Liverpool adverse-event profile (LAEP) were evaluated at baseline, 3, and 6 months and compared with healthy volunteers.
Results: Fenofibrate add-on therapy group had better seizure-control compared to baseline at 3 and 6 months (p value 0.023 and 0.007, respectively), though no significant difference with placebo group. The responder rate was high with fenofibrate (69.23%), compared to placebo (47.37%) group. There was significant increase in TAC in fenofibrate group at 6 months compared to baseline, while it was decreased in placebo group. The percentage change in neurotrophin-3 was higher in fenofibrate group than placebo group. Fenofibrate improved overall lipid-profile compared to placebo with decrease in total cholesterol, TG, LDL, and rise in HDL. In body composition and muscle strength assessment there was no significant changes. LAEP score was notably reduced in fenofibrate group compared to placebo group.
Conclusion: Better seizure control, increased TAC and improved lipid profile were observed after fenofibrate adjuvant therapy for 6 months. These findings suggest fenofibrate may have antiepileptogenic potential.

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Successful treatment of adult Dravet syndrome patients with cenobamate: encore abstract

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Purpose: Dravet syndrome (DS) is a rare, drug-resistant, severe developmental and epileptic encephalopathy caused by pathogenic variants in the α subunit of the voltage-gated sodium channel gene *SCN1A*. Hyperexcitability in DS results from loss of function in inhibitory interneurons. Thus sodium channel blockers are usually contraindicated in patients with DS as they may lead to disease aggravation. Cenobamate (CNB) is a novel antiseizure medication (ASM) with promising rates of seizure freedom in patients with focal-onset, drug-resistant epilepsy. CNB blocks persistent sodium currents by promoting the inactive states of sodium channels.
Method: In a multi-center study, we analyzed retrospectively the effect of an add-on therapy of CNB in adult patients with DS. Four patients were identified in four epilepsy centers and treated with CNB in 2021–2022. The retrospective analysis of epilepsy patient data was approved by the local ethics committees (approval nos. EA2/084/18 and 198/2010BO1).

Results: We report four adult patients with DS in whom the use of CNB resulted in a significant seizure reduction of more than 80%, with a follow-up of up to 542 days (median 428.5 days). In all patients the identified variants were predicted to be Loss of Function variants. CNB was the first drug in these patients that resulted in a long-lasting and significant seizure reduction. No severe adverse events occurred.
Conclusion: We highlight CNB as an ASM that may lead to a clinically meaningful reduction of seizure frequency in adult patients with DS. It is unclear, however, if all patients with DS benefit, requiring further investigation and functional experiments.[1] Due to the assumed mechanism of action, caution is required when initiating therapy with CNB in DS patients.

[1]Makridis, KL, Friedo, A-L, Kellinghaus, C, Losch, F-P, Schmitz, B, Boßelmann, C, et al. Successful treatment of adult Dravet syndrome patients with cenobamate. *Epilepsia*. 2022; 63: e164– e171. https://doi.org/10.1111/epi.17427

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Cannabidiol as add-on treatment in drug resistant epilepsy: real-life experience in a

tertiary centre

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Purpose: The efficacy and safety of Cannabidiol (CBD) were clearly established in clinical trials and open-label extension studies, yet data regarding real-life experience are scarce. The purpose of our study was to evaluate CBD safety and effectiveness in clinical practice in a tertiary center.
Method: We retrospectively included all patients referred to the Epilepsy Center at the IRCCS Istituto delle Scienze Neurologiche in Bologna, Italy, who received a CBD prescription (03/2019-12/2022). Patients were assessed at baseline, and after 3, 6 and 12 months. Patients were defined as "responders" and "super responders" if reporting a reduction in seizure frequency >30% and >80% compared with baseline, respectively. All adverse events reported were recorded to assess tolerability.
Results: 52 patients were included (mean age 38 years, range: 15-57; 17 females). In 46 patients CBD was prescribed on-label (Lennox-Gastaut syndrome, n=38; Dravet syndrome, n=5; tuberous sclerosis, n=3), while 6 patients were treated off-label (Lafora disease, n=3; Unverricht-Lundborg, n=1; polymicrogyria, n=1; febrile infection-related epilepsy syndrome, n=1). All patients were treated with at least other 2 ASM, including CLB. 42 patients had at least 3 months of follow-up: 56% of them achieved the ''responder'' or ''super responder'' categories at 3 months of follow-up (67% of the patients treated off-label), with sustained efficacy at 6 and 12 months. Twenty-two patients (53,6%) developed adverse effects, most frequently somnolence (15 patients, 36,5%) and diarrhea (4 patients, 9,8%). The retention rate was 70,8% at 12 months: 7 patients stopped treatment for persistent somnolence, 1 for having developed jaundice, and 4 for inefficacy
Conclusion: In this monocentric real-world trial, CBD was a safe and effective therapeutic option for highly drug-resistant patients, and, in a subset of these patients, determined a dramatic reduction in seizure frequency. The novelty and importance of this study is its contribution to gathering preliminary data about the off-label use of CBD.

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Intravenous brivaracetam in status epilepticus: a prospective study

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Purpose: Status epilepticus (SE) is defined as a seizure lasting longer than 5 minutes, or more than 1 seizure within a 5-minute period, without returning to a normal level of consciousness. It is one of the most important and life-threatening neurological emergencies. Refractory status epileptics (RSE) is not uncommon and may lead to brain functions impairment and decline in quality of life. The aim of this study is to evaluate the efficacy and tolerability of intravenous brivaracetam, a new antiseizure medication with higher permeability and a greater speed of action compared to levetiracetam, in refractory SE.
Method: 21 patients (15 woman; median age of 68,14 years ± 17,28) were prospectively recruited in a period of 30 months, from June 2019 to December 2022. Patients were treated with brivaracetam as an add on therapy for SE on an emergency context. Generally, the first line therapy was represented by intravenous diazepam or midazolam, according to the latest guidelines on SE.
Results: In detail, 20% of the examined patients had focal to bilateral epilepsy whereas 80% presented focal epilepsy. In 43% of patients the cause of SE was an underlying vascular pathology. We evaluated the early response of SE to the administration of brivaracetam and the recurrence of epileptic seizures after 12h and 24h from the administration of brivaracetam. 67% of patients displayed a good early response, while the remaining 33% did not respond to treatment.
Conclusion: The present study highlights the potential of brivaracetam when used as an add on therapy in refractory SE, especially if administered at early onset. It also proves its good safety profile, as none of the patients recruited in the study developed early or late side effects.

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May I, compare?

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Purpose: To assess and compare the effectiveness of the third-generation antiseizure medications (ASMs) brivaracetam (BRV), eslicarbazepine acetate (ESL), lacosamide (LCM) and perampanel (PER), in adult patients with epilepsy (PWE).
Method: Data from 22 Italian neurology/epilepsy centres were retrospectively collected. All adult PWE who started one of the studied drugs between January 2018 and October 2021 were included. Retention rates, described using Kaplan-Meier survival analyses, were used as overall measures of effectiveness. Both comparative and *per* drug dropout risks were estimated using an adjusted survival frailty model to account for clustering between centers and assuming an exponential hazard distribution (hazard ratio [HR] and 95% confidence intervals [CIs]).

Results: 960 patients (52.92% females, median age 43 years) met the inclusion criteria. The most prescribed ASM was PER (37%), followed by LCM (27.4%), BRV (25.2%), ESL (19.4%). The majority of patients had structural epilepsy (52.29%) and focal seizures (69.58%).
250 patients discontinued treatment mainly due to lack of efficacy (121 [48.4%]). The median withdrawal time was 8 months, and *per* drug dropout rates were: BRV [57.3%], ESL [30%], PER [28.7%], LCM [16.7%]). A statistically significant lower percentage of dropout was reported in patients treated with LCM compared with the others (Pearson chi-squared=19.6796, p=0.001). LCM showed the highest retention rate throughout the analysis time, especially in long-term follow-up (>80% at 36 months, whereas the other ASMs ranged from ~50% to 75%), but statistically significant differences in the hazard of dropout were not observed in the comparative estimates of the adjusted model.
Conclusion: Real-world data suggest higher retention rates in adult PWE treated with LCM, but the ASMs effectiveness seems to be affected by other factors different from the administered drug. A deeper understanding of these factors is mandatory, since it may help clinicians to identify the most appropriate drug for each patient.

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Efficacy and tolerability of cenobamate in add-on therapy in real clinical praxis. An observatory study from single epilepsy centre

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Purpose: Cenobamate is the latest antiseizure medication (ASM) authorized for the treatment of focal onset seizures. This drug inhibits the persistent, rather than transient, voltage-gated sodium channel currents and is a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors, differently from benzodiazepines. It was marketed in Slovakia in Auguste 2022. Aim of this study was to analyse the efficacy and tolerability of cenobamate in real clinical praxis.
Method: Observational study of a cohort of 20 patients (10 women and 10 men), who were treated with cenobamate as add-on therapy since Auguste 2022, up to four month. Mean age was 32,9 y, mean epilepsy duration 20,7 y, mean number of failed ASM was 9, mean number of ASM to which cenobamate was added was 2,85.
Results: Four patients (20%) were seizure free in the observation period, seven (35%) achieved more than 50% reduction of the seizures. Mean seizure frequency reduction was -30,8% and median seizure frequency reduction was -33,3%. Cenobamate was withdrawn in six patients due to adverse events (TAE)(30%). The TAE were: somnolence, aggitation, worsening of the seizures, abnormal self perception, rash, fatigue, urinary retention, periictal psychosis, lymph nodes swelling, headache and diarrhea, all disappeared after drug discontinuation.
Conclusion: Treatment of drug resistant epilepsy is still challenging. Our early results are in accordance with data available yet. More patients enrolment and longer follow-up is on the

way.

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Predicting pharmacokinetic interactions of enzyme-inducing antiseizure medications: to what extent can we use the data on their interactions with sensitive CYP3A4 substrates?

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Purpose: Antiseizure medications (ASMs) can induce the elimination of many drugs that are cytochrome P450 (CYP) 3A4 substrates. It has been suggested that the newer ASMs are safer regarding CYP3A4 induction. However, it is currently unknown whether the ASM ability to enhance the elimination of sensitive CYP3A4 substrates predicts their ability to reduce exposure to other drugs. This analysis aimed to correlate the ASM induction potential for sensitive CYP3A4 substrates with that of oral contraceptives and P-gp or dual CYP3A4/P-gp substrates. **Method**: PubMed, Embase and Cochrane Library were searched up to December 2022 without date restriction to examine all works representing drug interaction between ASMs and relevant substrates. Studies had to be in humans and indicate a change in AUC or clearance of the drugs when given in combination with ASMs. Case reports were excluded. We additionally searched the FDA's Clinical Pharmacology and Biopharmaceutics Review for each ASM. The primary parameter was the [substrate+ASM]/[substrate only] AUC ratio (AUCR). The AUCR correlations were evaluated using Spearman analysis. AUCR. PROSPERO registry number: CRD42022335846.

Results: The correlation between the median AUCR involving sensitive CYP3A4 substrates and that of oral contraceptives was modest ($r=0.59$, $p>0.05$) and improved upon categorization by the ASM dose ($r=0.75$, $p<0.05$). Oxcarbazepine was an outlier, having a more significant impact on contraceptives AUCR than predicted by its CYP3A4 induction. The correlation for P-gp- or dual P-gp/CYP3A4 P-substrates was highly affected by the phenobarbital data. **Conclusion**: The magnitude of change in exposure to sensitive CYP3A4 substrates may be used to predict the ASM effects on less sensitive substrates. We are currently analyzing data on additional moderately-sensitive CYP3A4 substrates, P-gp substrates, and substrates of other enzymes and transporters co-induced with CYP3A4, to better understand to what extent the data can be generalized to other drug groups, considering the distinct induction pathways.

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Effect of patient-related factors on brivaracetam efficacy and tolerability: results from a multicentric, retrospective study

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Purpose: To assess the contribution of patient-related factors to influencing treatment response and adverse events (AEs) occurrence in patients with drug-resistant epilepsy (DRE) treated with brivaracetam (BRV).
Method: A multicentric, retrospective study collecting data from all adult patients with DRE who started BRV as part of routine clinical practice. Multivariate logistic models (odds ratios [ORs] and 95% confidence intervals [CIs]) were used to explore the contribution of age, sex, causes of epilepsy, follow-up duration, disease duration, number of previous therapeutic attempts, number of concomitant antiseizure medications (ASMs), on treatment response (reduction ≥50% in seizure frequency plus seizure-freedom) and AEs occurrence.
Results: 242 patients (165 [68.2%] naïve to levetiracetam [LEV], 53%, females, mean age 43.6 [±17.3 SD] years) were included. They mainly suffered from structural epilepsy (n=121 [50%]), with focal (n=173 [71.5%] seizures of monthly frequency (n=95 [39.2%]).
During the follow-up (ranging from 0 to 36 months), 39/242 patients experienced at least one AE (none of them serious), which led to treatment discontinuation in 18/39 cases; at last available follow-up, 111/242 patients were responders.
Multivariate analysis showed that patients naïve to LEV had a significantly reduced probability of treatment response as the number of previous ASMs increased (OR 0.44; CI 0.25-0.80, p=0.007), whereas the response probability was significantly higher for female patients compared with males (OR 12.99; CI 2.35-71.73, p=0.003). There were no factors significantly affecting the likelihood of AE occurrence.
Conclusion: Our data confirm the overall good efficacy and tolerability profile of BRV in adult patients with DRE and suggest some efficacy predictors in those naïve to LEV. Number of previous ASMs and female sex seem to be associated with a lower and a higher likelihood of achieving treatment response, respectively. However, results from larger cohorts and prospective studies are needed to confirm the data.

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Effect of fenfluramine on generalized tonic-clonic seizures in rare epilepsy syndromes: a review of published studies

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Purpose: We aim to describe the effectiveness of fenfluramine (FFA) on generalized tonic-clonic seizures (GTCS) or tonic-clonic seizures (TCS) in patients with rare epilepsy syndromes.
Method: Reports of patients treated with FFA for seizures associated with rare epilepsy syndromes were identified and included if FFA was used for convulsive seizure control. The studies selected described a change in the frequency of GTCS, TCS, or major motor seizures. Case reports or studies where the reduction in GTCS or TCS was unclear were excluded. Initial FFA doses, duration of treatment (exposure), and reduction in GTCS/TCS are reported. Descriptive statistics were used.
Results: We included data from 13 studies: 4 randomized-controlled trials (RCTs), 4 observational studies, 4 open-label studies, and 1 case series. In these studies, 561 patients were treated with FFA for DS (n=360), LGS (n=176), Sunflower syndrome (n=10), CDKL5 deficiency disorder (n=6), *SCN8A*-related disorder (n=3), and other developmental and epileptic encephalopathies (DEEs; n=6). Of these, 396 (70.6%) patients experienced GTCS or TCS at baseline. FFA was generally initiated at 0.2 mg/kg/day and titrated per protocol or physician discretion; mean/median FFA exposure: 12 weeks-16 years. In 3 studies, the reduction in GTCS or TCS was included as part of the overall seizure type evaluated. In 8 studies (including the 4 RCTs), the median percent reduction in GTCS ranged from 45.7%-90.8%. Among 8 studies providing data, 7 reported at least half of the patients experienced ≥75% reduction in GTCS or TCS; five studies reported more than half of patients were GTCS-free after FFA treatment.
Conclusion: These results indicate that FFA led to a clinically significant reduction in GTCS or TCS frequency in patients with rare epilepsy syndromes. Further research is needed to determine the impact of FFA on sudden unexpected death in epilepsy (SUDEP) in those patient populations. Funded by UCB Pharma.

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Design of a phase 3 clinical study to examine the efficacy and safety of fenfluramine (ZX008) in subjects with CDKL5 deficiency disorder followed by an open-label extension

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Purpose: To describe the ongoing 2-part multicenter trial of adjunctive ZX008 in subjects with CDKL5 deficiency disorder (CDD) and uncontrolled seizures (NCT05064878).
Method: Part 1 will evaluate efficacy and safety of fixed-dose ZX008 in a 20-week randomized, placebo-controlled study; Part 2, a 54-week open-label extension (OLE), will evaluate long-term effectiveness and safety. Caregivers must report ≥4 countable motor seizures/week and ≥1 concomitant antiseizure treatment. Exclusion criteria include pulmonary arterial hypertension (PAH) or history of cardiovascular or cerebrovascular disease. Subjects will be randomized to ZX008 0.8 mg/kg/day (max=30 mg/day), ZX008 0.5 mg/kg/day if concomitant stiripentol (max=20 mg/day), or placebo. In the OLE, subjects will start ZX008 at 0.2 mg/kg/day; adjusted for effectiveness and tolerability after ≥1 month. Quantity, type, and duration of seizures, rescue use, and dosing will be recorded in an e-diary. Electrocardiograms and 2-D Doppler echocardiograms will evaluate cardiac safety.
Results: Approximately 80 subjects (2-35 y) with CDD will be recruited. After an interim safety review, subjects 1 to <2 y will be enrolled. Seizure and non-seizure efficacy endpoints for both parts will include: median percentage change in monthly countable motor seizure frequency (CMSF) from baseline vs placebo (part 1) and over the entire OLE treatment period (part 2); proportion of subjects achieving 0%, ≥25%, ≥50%, ≥75%, or 100% reduction from baseline in CMSF; percentage of subjects with improvement in the Clinical Global Impression-Improvement rating scale assessed by investigators and caregivers; change from baseline in subject's quality of life (QOL; QI-Disability) and caregiver's QOL (EQ-5D-5L); changes in subject's sleep behavior. Safety endpoints will include incidence of adverse events, increase in valvular regurgitation from baseline, and occurrence of PAH.
Conclusion: This study will characterize the efficacy and safety of ZX008 for treatment of seizures associated with CDD, providing an opportunity to address an unmet medical need.
Funded by UCB Pharma.

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Effectiveness of Cannabidiol in Epileptic Syndromes besides Dravet and Lennox Gastaut: real-world evidence from a level 3 epilepsy center

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Purpose: The highly purified CBD oil (Epidiolex) is licensed as adjunctive antiseizure treatment in patients with Dravet(DS) or Lennox Gastaut(LGS) syndromes and Tuberous-Sclerosis-Complex[1]. Nevertheless, evidence about CBD effectiveness in other Developmental and Epileptic Encephalopathies(DEEs) have been provided in few cases[2]. The aim of our study was to assess the effectiveness of CBD as adjunctive treatment in a cohort of patients with DS, LGS and other drug-resistant epileptic syndromes, particularly genetic DEEs.
Method: We conducted a 12 months observational prospective clinical trial. We enrolled 13

patients (aged 13-52 years) affected with drug-resistant epilepsy of different etiology. Patients received CBD 5mg/kg/day for two weeks, then titrated up to 20 mg/kg/day. Seizures' frequency, EEG and blood exams were assessed at 3, 6 and 12 months. Further effects were evaluated by QOLIE-10P, QOLCE, Pittsburgh and Epworth Scales, BDI-II, PGIC, CGIC. The primary endpoints were responder rate and safety in our cohort.
Results: Three patients presented with LGS, three with LGS-like phenotype (one due to dupXq28), one with Febrile-Infection-Related-Epilepsy-Syndrome, one with DS, five with other genetic DEEs (of these one related to *MEF2C*, one to *PCDH19*, and one to *STXBP1*). Whole-Exome-Sequencing is ongoing in 4 patients with no genetic diagnosis to date.
Nine patients concluded the 12 months study; two discontinued CBD after one month owing to lack of compliance, the patients with *STXBP1* and *MEF2C*-related DEE discontinued after six and ten months respectively owing to lack of efficacy. We observed reduction in seizure's frequency at 12 months in all the nine patients who completed the study, of the 50% or greater in 6/9 patients(66,7%). Seizure freedom was achieved in two patients, including the individual with *PCDH19*-related DEE. No serious AEs were registered; the most frequent was somnolence.
Conclusion: CBD adjunctive antiseizure treatment is effective and well tolerated in DEEs beyond LGS and DS and, particularly in *PCDH19*-related-DEE.

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Six-month efficacy data for Cenobamate in refractory focal epilepsy – a viable alternative to VNS?

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Purpose: To assess the efficacy of adjuvant Cenobamate in adults with refractory focal epilepsy.
Method: A retrospective cohort study was conducted. Patients were commenced on adjuvant Cenobamate between January and June 2022; reduction in seizure frequency and change in concomitant antiseizure medications (ASMs) was assessed over a six-month period.
Results: Of 43 patients (23 male), 40 had a seizure duration of over 10 years. 18 patients (41 %) had intellectual disability. 35 patients were on the surgical pathway, over 50% having undergone or awaiting VNS. 71% of patients were prescribed at least three concomitant ASMS at baseline.
38 patients tolerated Cenobamate for six months. Of these, 36 achieved a reduction in seizure frequency with a dose of Cenobamate of 50-200mg/day. 19 patients (50%) achieved significant seizure reduction (over 50%), of whom 3 were seizure free.
16 patients (42 %) were able to withdraw one concomitant ASM. 2 patients were able to withdraw two ASMs.
Conclusion: Thus far, adjuvant Cenobamate reduces seizure burden in the majority of patients with severe refractory focal epilepsy. It may be a viable alternative to VNS in those pa-

tients who have limited options accessing a surgical pathway.

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A Phase 1 Clinical Study Shows Robust LP352 CSF Exposures Supporting Dose Optimization for 5-HT2C Receptor Engagement

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Purpose: To evaluate the CSF pharmacokinetics relative to the 5-HT2C binding constant (Ki) of LP352, a highly selective 5-HT2C superagonist being developed for treatment of developmental and epileptic encephalopathies (DEEs), in comparison to lorcaserin, a 5-HT2C agonist having shown seizure reduction in DEE.
Method: Healthy adult subjects (18-55 years; n=20) received LP352 in a liquid formulation (3 mg/mL) at 6 mg TID and 12 mg TID for 8 days. Serial CSF samples were taken at steady state and compared to the in vitro Ki value of LP352 required to elicit 5-HT2C agonism. Data from this study were compared to published lorcaserin Ki and CSF data (10 mg, BID).
Results: LP352 exhibited dose linear and consistent CSF pharmacokinetics. The mean CSF Cmax,ss and Cave,ss values were 12.29 ng/mL and 9.26 ng/mL for 6 mg TID and 30.36 ng/mL and 24.36 ng/mL for 12 mg TID, respectively. The mean AUC_{tau} values were 74.06 hr*ng/mL for 6 mg TID and 194.88 hr*ng/mL for 12 mg TID. Lorcaserin's previously reported values for Cmax,ss, Cavg,ss and AUC_{tau} were 0.95 ng/mL, 0.78 ng/mL and 9.31 hr*ng/mL, respectively.
Conclusion: Both doses of LP352 resulted in robust CSF concentrations with potential for clinically meaningful engagement of 5-HT2C receptors. LP352 showed likely greater engagement than lorcaserin, based on the CSF exposure relative to Ki values. The mean Cavg,ss CSF concentrations of LP352 at 6 and 12 mg TID reached approximately 0.6-fold and 1.7-fold of the Ki value (14.4 ng/mL) for 5-HT2C agonism, whereas the Cavg,ss CSF concentration for lorcaserin reached only approximately 0.3-fold of the Ki value (2.5 ng/mL) at a 10 mg BID dose. These data support that LP352 achieves relatively high CSF levels vis-à-vis the Ki, and may offer the opportunity to optimize dosing for safety and efficacy during LP352's clinical development.

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Evaluation of Prolactin as a Useful Pharmacodynamic Tool to Assess Engagement of Central 5-HT2C Receptors by LP352, a Potent and Selective 5-HT2C Agonist

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Purpose: Converging lines of evidence indicate prolactin elevations in response to serotonergic agonists reflect drug-induced activation of 5-HT2C receptors in the central nervous system. Therefore, serum prolactin may represent a useful pharmacodynamic tool for evaluating the engagement of central 5-HT2C receptors. LP352, in development for the treatment of developmental and epileptic encephalopathies, is a potent and selective 5-HT2C receptor

agonist, showing selectivity for the 5-HT2C receptor versus 5-HT2A and 5-HT2B. The purpose of this analysis is to assess serum prolactin changes in response to LP352 administration.
Method: Serum prolactin levels were evaluated in single (SAD) and multiple (MAD) ascending dose studies of LP352. Both were randomized, double blind, placebo-controlled studies in healthy volunteers. The SAD study contained 6 arms: single oral doses of 1, 3, 6, 12 or 24 mg (n=6) or placebo (n=10). The MAD study contained 5 arms: 3, 6, 12, or 18 mg LP352 administered TID (n=6) or placebo (n=8). Prolactin serum concentrations were summarized by timepoint and dose, with predose serum prolactin values on Day 1 considered baseline values. Fold change from baseline was calculated against the maximum prolactin level at 2 hours post-dose on Days 1 and 14.
Results: Prolactin demonstrated an acute dose-dependent increase at 2 hours following single LP352 doses, as well as after the first dose of the 14-day multiple dose regimen. In addition, Day 14 evaluation of prolactin did not demonstrate any differences between LP352 and placebo. No subject reported an adverse event attributable to hyperprolactinemia (e.g., galactorrhea, gynecomastia).
Conclusion: These data suggest LP352 engages central 5-HT2C receptors at physiologically relevant concentrations and support the suitability of prolactin as a biomarker of 5-HT2C agonism in the early dosing period. The attenuation of response on Day 14 suggests the prolactin increase elicited by LP352 activation of 5-HT2C receptors is transient.

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Antiseizure medication safety in pregnant people for non-epilepsy conditions

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Purpose: Antiseizure medication (ASM) exposure in utero has been associated with an increased risk of adverse birth outcomes. With the increase in the use of ASMs for off-label indication in the last two decades, there is a need for ASMs safety research in pregnant people without epilepsy (PPWOE).
Method: We conducted a population-based cohort study among pregnant people in Manitoba, Canada from 1998 to 2019. We examined the association between ASMs and the risk of small for gestational age (SGA), low birth weight (LBW), preterm birth, NICU admissions, length of hospital stay (LOS) (> 3 days) in mothers, LOS infants, infant mortality, neonatal mortality, and neonatal readmissions in PPWOE. Multivariate regression models were adjusted for pain diagnoses, psychiatric disorders, diabetes, hypertension, urban/rural, socio-economic status and teratogenic drugs.
Results: We analyzed 2893 ASMs exposed PPWOE and 267712 unexposed pregnant people. In ASMs exposed PPWOE, we found a significant increased risk of LBW (aOR 1.54, 95%CI 1.34), preterm birth (aOR 1.52, 95%CI 1.35-1.71), NICU admissions (aOR 1.96, 95%CI 1.76-2.18), LOS(mother) (aOR 1.14, 95%CI 1.04-1.25), LOS (Infant) (aOR 1.61, 95%CI 1.47-1.76) and

a non-significant increase in SGA (aOR 1.13, 95%CI 0.99-1.28), infants mortality (aOR 1.22, 95%CI 0.78-1.92), neonatal mortality (aOR 1.32, 95%CI 0.76-2.29) and neonatal admissions (aOR 1.05, 95%CI 0.85-1.28) when compared with unexposed pregnant people.
Conclusion: ASMs exposure was associated with an increased risk of several adverse birth outcomes in PPWOE. Therefore, prescription of ASMs for non-epilepsy indication must be rationalized, especially when alternate treatments can be safer for pregnant people.

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Frequency of epilepsy onset after discontinuation of preventive epilepsy treatment in tuberous sclerosis complex (TSC)

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Purpose: Preventive treatment with vigabatrin (VGB) improves epilepsy outcome and neurodevelopment in patients with tuberous sclerosis complex (TSC). However, there is insufficient knowledge on the longstanding effects after successful discontinuation of the treatment. This study evaluates the long-term outcomes of preventive treatment with vigabatrin after pharmacotherapy cessation.
Method: Retrospective review of children treated preventively in the first 2 years of age with vigabatrin. The data were collected from two clinical centers: The Children's Memorial Health Institute, and the Medical University of Warsaw in Warsaw, Poland.
The inclusion criteria were: 1/patients with TSC who obtained preventive treatment with vigabatrin within 24 months of age, 2/ discontinuation of the treatment with all antiepileptic drugs (AEDs), 3/ follow-up after treatment removal at least 12 months.
Results: Seventeen patients were included in the study, 8 females and 9 males. All participants were treated preventively with vigabatrin due to paroxysmal epileptiform activity on EEG.
Vigabatrin was introduced at the median age of 175 days (8-766 days). The median treatment duration was 2.9 years (1.7-6.7 years) in all patients.
During the preventive treatment period with VGB 15 out of 17 (88.2%) children remained seizure-free. In 2 infants, despite of the treatment, appeared seizures but dissolved after drug modification. In those who remained seizure free till 24 months of age or had controlled seizures at least 2 years, the decision of drug withdrawal has been taken (17 children).
During the median 2.5 years (1.2-12.3 years) follow-up after drug withdrawal epilepsy was reported in 1 out of 17 (5.9%) children. Sixteen out of 17 (94.1%) remained seizure-free and treatment-free.
Conclusion: In the vast majority of patients with TSC seizure control continues after discontinuation of the preventive treatment with vigabatrin during median follow-up. However, the median time of observation in the study was 2.5 years and results require further studies.

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Elektroencephalographic evaluation of cenobamate in refractory epilepsies

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Purpose: In refractory epilepsies, it is not unusual to find an increased rate of subclinical ictal activity in the routine EEG practice. The efficacy of cenobamate in patients with refractory epilepsies has been demonstrated, while a thorough electoencephalografic evaluation of this substance has not been performed yet. The objective was to evaluate the effect of cenobamate on the ictal activity in routine EEG.
Method: Immediately prior to the initiation of the anti-seizure therapy with cenobamate, a baseline EEG was performed in each of the participants of this study, with a follow-up EEG after 6 months. Only those participants with interictal epileptiform discharges or subclinical seizures in their baseline EEGs were included in the study. Those with a clinical seizure in the last 24 hours prior to the EEG recording were excluded.
Results: We included 34 patients with a mean age of 41.2 years. In the baseline EEG, Interictal epileptiform discharges were recorded in 26 participants (76,5%) and subclinical seizures in 8 participants (23.5%) . Most of the participants were treated with 200mg/day. In the electoencephalograpy at 6-month follow-up, there was a substantial decrease in the rate of interictal epileptiform discharges (23,5%) as well as the subclinical seizures (8,8%). Cenobamate resulted in a responder rate of 58,8%, which was defined as a reduction of seizure frequency by at least 50% The seizure freedom was observed in 23.5% of the participants.
Conclusion: Besides its clinical efficacy in reducing the seizure frequency, cenobamate seems to be a promising antiseizure medication suppressing the subclinical ictal activity in EEG such as interictal epileptic discharges and subclinical seizure patterns.

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Use of lacosamide for acute symptomatic refractory seizures in neonates

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Purpose: No evidence-based guidelines exist for the pharmacological management of neonatal seizures. Few medications have been studied in controlled trials. The use of lacosamide as treatment in refractory seizures has been increasingly reported in newborns, but efficacy and safeness hasn't been described. The aim of this study is to describe its use, efficacy, and safeness.
Method: All patients admitted between 2018 and 2022 in the NICU with diagnosis of symptomatic acute refractory seizures were enrolled in a prospective descriptive study. Lacosamide is considered a third-line treatment in our unit in newborns with non-respondent symptomatic focal seizures. Dose, duration and response to treatment is described. Regarding

follow up, GMFCS scale and developmental quotient-scores were collected.-
Results: 7 patients were enrolled among 62 with the diagnosis. The etiologies were meningitis (2/7), venous sinuous thrombosis (1/7), infarct (2/7), and polymicrogyria (2/7). Median gestational age was 40.3(38-40.5). All patients had electro-clinical seizures [focal-clonic (5/7) or autonomic (2/7)], starting at a median of 33(16-576) hours of life.
Lacosamide was used as 3rd/4th line of treatment. All cases received a loading dose, 3/7 patients only received this, in the others treatment was continued.5/7 patients showed seizures remission after the loading dose and didn't relapse during follow-up. The patients with polymicrogyria needed hemispherectomy or barbiturate-induced-coma to achieve remission. No adverse effects were described.
6/7 patients completed follow up for a median of 24 months (11-48). There are 2 patients with normal development, 1 hearing loss, 1 hemiparesis with normal cognitive development and 2 global developmental delay with cerebral palsy. Results are concordant with MRI and expectations.
Conclusion: We report 5 cases were lacosamide was effective (70%) for seizure remission without posterior relapse. Only two cases with polymicrogyria hadn't response. No side effects and good results in long-term outcome were reported. Further studies are needed to confirm these preliminary results.

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Challenges in conducting an academic international European multicentre trial: what we can learn from the RESCUE ESES trial

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Purpose: Randomised controlled trials (RCTs) are the "gold-standard" for safety and effectiveness assessments but are particularly challenging in rare diseases. Epileptic encephalopathy with spike wave activation in sleep (EE-SWAS) is a rare childhood epilepsy syndrome which can lead to devastating developmental deficits. Evidence on the most effective treatments is lacking and a group of European experts designed a multicentre trial to reflect existing medical practices. We present the challenges conducting an international multicentre trial.
Method: A European multicentre randomised controlled trial in children with EE-SWAS (RESCUE ESES) was performed between 2013 and 2022 and aimed to compare effects of treatment with corticosteroids or clobazam in 130 children with EE-SWAS aged 2 to 12 years.
Results: Trial initiation was delayed at many sites by the need to address heterogeneous procedures by ethical committees and competent authorities working under different regulations and conditions. Approval of the study protocol and documents and setting-up clinical

trial agreements was very time consuming. Although for routine clinical care both study drugs are readily available, these drugs had to be imported and labelled specifically for the trial at several study sites. Initially, principal investigators of 21 centres intended to participate. Complying with regulatory requirements sometimes proved to be practically unfeasible and 5 sites were never initiated. Although pre-trial feasibility survey results suggested that more than sufficient patients would meet inclusion criteria, actual recruitment was hampered for many reasons, including parental or doctor's treatment preferences. Eventually only 7 sites enrolled patients. Despite repeatedly extending the study, enrolment was stopped prematurely for feasibility reasons after inclusion of only 45 patients.
Conclusion: Investigator-driven RCTs in rare diseases are highly challenging. The lessons learned in this trial are of importance to all centres taking part in international multicentre studies. We strongly advocate to simplify and harmonise regulations and centralise regulatory assessment of investigator-driven trials.

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Anti-epileptic and pro-cognitive effects of GAO-3-02 are associated with enhanced GABAergic transmission and anti-inflammatory action

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Purpose: GAO-3-02, a derivative of the endocannabinoid N-docosahexanoylethanolamide (synaptamide), has been developed not only to control seizures but also to improve associated cognitive impairments. In this study, we examined: 1) the anti-seizure effect of GAO-3-02 in acute and chronic models of epilepsy; 2) its protective effect on hippocampal long-term potentiation (LTP), a cellular mechanism underlying learning and memory, in a rat model of temporal lobe epilepsy (TLE); and 3) its potential mechanism of action, by investigating its impact on GABAergic transmission and inflammation.
Method: GAO-3-02 administered p.o. was tested on acute seizures induced in mice by pentylenetetrazole (PTZ) and in two models of TLE with chronic seizures, induced either in mice after intrahippocampic kainic acid (KA) injection or in rats following pilocarpine-induced status epilepticus (Pilo-SE) at weaning. LTP induction was measured in CA1 pyramidal cells in the presence or absence of GAO-3-02 directly applied on hippocampal slices from epileptic rats. The effect of GAO-3-02 on GABAergic neurotransmission was also investigated in slice from epileptic rats by measuring the amplitude of evoked inhibitory postsynaptic currents (eIPSCs). Finally, the anti-inflammatory effects of GAO-3-02 were evaluated in the Pilo-SE model at the peak (9H post-SE) of inflammation (GAO-3-02 administered 2-5 mg/kg i.p. 2h post-SE) and in murine microglial cell lines (BV2) treated with lipopolysaccharide (LPS).
Results: GAO-3-02 dose-dependently protected against PTZ-induced seizures, and reduced seizure frequency in Pilo-SE rats and paroxysmal hippocampal discharges in mice subjected

to intrahippocampic KA. Bath-application of GAO-3-02 reversed hippocampal LTP deficits and significantly increased eIPSCs in slices from epileptic rats. Finally, GAO-3-02 significantly reduced inflammatory response following Pilo-SE in rats (IL1β and TNF) and LPS-treated BV2 cells (IL1β, IL6, TNF, NOS2, COX2).
Conclusion: Overall, GAO-3-02 displayed antiseizure and procognitive effects in acute and chronic seizure models likely through an increase in GABAergic transmission and a reduction in inflammatory status.

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In vivo effects of a novel series of antisense oligonucleotide targeting microRNA-134 in experimental temporal lobe epilepsy

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Purpose: Drug-resistance remains a major hurdle for clinical management of epilepsy. RNA therapeutics comprise an emerging drug modality for the treatment of neurological disorders. Antisense oligonucleotides and RNA drugs can be utilised to modulate targets (mRNAs and non-coding RNAs) previously deemed undruggable. MicroRNAs are small noncoding RNAs that have emerged as potential targets for the treatment of epilepsy. The multi-targeting actions of miRNAs, wherein an individual miRNA can target dozens of different mRNAs, may be uniquely relevant for treating the complex pathophysiology that drives development and maintenance of acquired epilepsies such as temporal lobe epilepsy.
We have previously shown that an ASO design to inhibit miR-134 (antimir-34) has potent anti-seizure effects in rodents. Here, we explored a new series of antimirs designed against this target, and demonstrate proof-of-concept *in vivo* efficacy in intra-amygdala kainic acid mouse model
Method: Adult male mice were subjected either to an ICV injection of ASOs (NMC-1, NMC-2 or the original "antimir-134") for evaluation of knockdown of the miRNA or first to status epilepticus (SE) induced by intra-amygdala microinjection of KA followed by ICV injection of the antimirs. Control mice received PBS instead of antimirs. Digitized EEG recordings and SRS counts were analyzed offline. Levels of miRNAs were assessed by qPCR using Taqman miRNA assays.
Results: The ASOs NMC-1 and NMC-2 potently suppressed levels of target miRNA in the hippocampus of mice. NMC-1 showed similar potency to antimir-134 and was superior to NMC-2. Mice treated after SE with NMC-1 and original antimir-134, but not NMC-2, showed a ~50% reduction in the occurrence of SRS
Conclusion: The studies demonstrate the potential of the additional antimir ASO designs to target miR-134 in vivo and produce potent anti-seizure effects. These ASO drugs may be suit-

able for further preclinical development including exploring their ability to reverse already-established epilepsy in mice.

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Design of a double-blind, randomized, placebo-controlled phase 2 trial of Darigabat as adjunctive therapy in adults with drug-resistant focal onset seizures (REALIZE)

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Purpose: Darigabat (CVL-865) is a novel α2/3/5 subunit–selective γ-aminobutyric acid A receptor ($GABA_AR$)–positive allosteric modulator (PAM). Darigabat is structurally distinct from benzodiazepines and is designed to avoid dose-limiting negative effects typically associated with benzodiazepine activity at $GABA_AR$ α1-subunits (e.g., sedation). We describe the design of an ongoing phase 2 trial assessing darigabat in drug-resistant focal epilepsy.
Method: REALIZE (NCT04244175) is a global, double-blind, parallel-group, placebo-controlled trial enrolling adults aged 18-75 years diagnosed with focal epilepsy for ≥2 years, history of ≥4 spontaneous seizures/month for ≥3 months prior to screening, prior failure of ≥2 antiseizure medications, currently taking 1-3 permitted antiseizure medications, and ≥8 focal seizures during an 8-week baseline period. Participants are randomized 1:1:1 to placebo, 7.5-mg darigabat twice daily, or 25-mg darigabat twice daily for 13 weeks (2-week titration, 8-week maintenance, 3-week taper) followed by a 4-week safety follow-up. Eligible participants may continue treatment in a 57-week open-label extension (NCT04686786) after the maintenance phase. COVID-19 mitigation included remote data collection and remote visits for prespecified time points and assessments.
Results: Planned enrollment of 150 participants is ongoing (completion anticipated this year). Most enrolled participants have completed the trial and rolled over to the openlabel extension. The primary endpoint is reduction in focal seizure frequency, calculated as a response ratio of seizure frequency/week during maintenance versus baseline period. Secondary endpoints include change from baseline in weekly focal seizure frequency and percentage of participants with ≥50% reduction in focal seizure frequency. Safety and tolerability assessments include the Modified Clinical Institute Withdrawal Assessment-Benzodiazepines. Sample size will provide ≥80% power to detect a ≥30% reduction in seizure frequency (two-sided alpha level of 0.10).
Conclusion: This trial will characterize the efficacy and safety profile of the α1 subunit–sparing $GABA_AR$ PAM darigabat in adults with drug-resistant focal epilepsy. This trial is funded by Cerevel Therapeutics.

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Monarch and Admiral interim analyses: ongoing, open-label, phase 1/2a studies in us and UK investigating safety and drug exposure of stk-001, an antisense oligonu-

cleotide (ASO), in children and adolescents with Dravet syndrome (DS)

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Purpose: DS is a severe and progressive genetic epilepsy and approximately 85% of cases are caused by heterozygous, loss of function, *de novo* mutations in the *SCN1A* gene, which encodes the $Na_v1.1$ protein. DS is characterized by high seizure frequency (SF) and severity, intellectual disability, and ataxia/motor abnormalities. STK-001 designed to upregulate $Na_v1.1$ brain protein expression by leveraging the wild-type (non-mutant) copy of *SCN1A* to restore physiological $Na_v1.1$ levels, thereby potentially reducing both SF and non-seizure comorbidities.
Method: MONARCH (NCT04442295) and ADMIRAL (2020-006016-24) are studies of patients with DS aged 2-18 years assessing safety, tolerability, plasma PK and CSF exposure of intrathecally (IT) administered ascending doses of STK-001. Patients have disease onset <12 months old with recurrent seizures and a confirmed clinically relevant *SCN1A* variant. Patients are grouped by age (2-12 and 13-18 years) and SF is observed for 28 days before dosing and followed for 6 months after last dose. AEs are monitored continuously, with plasma and CSF collected for STK-001 exposure at multiple times.
Results: As of 11AUG22, 55 patients received ≥1 STK-001 (10-45mg/dose). All treatment-emergent AEs related to study drug were non-serious and mild or moderate. 74.1% (20/27) of patients treated with 3 doses experienced a reduction from baseline in convulsive SF from Day 29 after 1st dose to 3-month post last dose. 55.2% median reduction was observed in patients treated with 45mg (n=6). SF reductions occurred on a background of anti-seizure medications, including fenfluramine. Dose-dependent increase in plasma and CSF exposure was observed, and following repeat dosing, CSF STK-001 accumulation was observed.
Conclusion: Data indicate that STK-001 was well-tolerated and overall potential benefit-risk remains favorable in single and multiple doses up to 45mg/dose. Data support continued STK-001 development as the first potential disease-modifying approach to treat DS. These data will help inform future STK-001 clinical studies.

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SWALLOWTAIL: An open-label extension (OLE) study for children and adolescents

with Dravet syndrome (DS) who previously participated in a study of antisense oligonucleotide (ASO) STK-001

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Purpose: DS is a severe and progressive genetic epilepsy that typically begins in the first year of life. Approximately 85% of cases are caused by heterozygous, loss of function, *de novo* mutations in the *SCN1A* gene, which encodes the voltage-gated sodium channel type 1 α subunit ($Na_v1.1$) protein. DS is characterized by high seizure frequency (SF) and severity, intellectual disability, and gait/motor abnormalities. STK-001 is an investigational ASO treatment designed to upregulate $Na_v1.1$ protein expression in the brain by leveraging the wild-type (non-mutant) copy of *SCN1A* to restore physiological $Na_v1.1$ levels, thereby potentially reducing both SF and non-seizure comorbidities.
Method: SWALLOWTAIL (NCT04740476) is a US ongoing multi-center OLE study, assessing the long-term safety, tolerability, plasma and CSF exposure and clinical effect of repeat doses of STK-001 administered every 4 months by intrathecal (IT) injection in patients who completed MONARCH (NCT04442295), a Phase 1/2a study of STK-001. Adverse events (AEs) are monitored continuously, and CSF and plasma samples are collected at each visit. Clinical assessments including SF, neurodevelopmental status, gait, and executive functioning are evaluated.
Results: As of 11Jul2022, 96% patients (24/25) who completed MONARCH enrolled in SWALLOWTAIL. Patients received up to 5 STK-001 doses given every 4 months (10-45mg/dose). All treatment-emergent AEs related to study drug were non-serious and mild or moderate. Dose-dependent increase in CSF Ctrough levels was observed from 20–30mg across all cohorts. In patients administered 30mg (n=4), reductions in convulsive SF that were observed in MONARCH were maintained with ongoing treatment and a trend toward improvement in executive functioning (BRIEF-P) was observed in SWALLOWTAIL.
Conclusion: Data support continued STK-001 development as the first potential disease-modifying approach to treat DS. SWALLOWTAIL will inform on the long-term safety and tolerability of repeat administration and will help inform future STK-001 clinical studies.

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Epilepsy characterization in a group of children with microcephaly and Zika associated birth defects: descriptive analysis of a 5-year follow-up in two Colombian cities

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Purpose: To characterize epilepsy patterns in a group of children with microcephaly and Zika-associated birth defects (MZABD) during the first 5 years of life
Method: Longitudinal descriptive study. Biannual follow-up from 2017 (median age: 8 months) to 2022 (median age: 66 months), of children with MZABD. Data related to epilepsy were analyzed. Data from children diagnosed with early-onset epilepsy (EoE) and late-onset epilepsy (LoE) (before and after the first year of life, respectively) was compared.
Results:
Data from 26 children were analyzed, 92.3% were diagnosed with epilepsy. 70.8% presented EoE, and 29.2% LoE. The most frequent types of epilepsy in EoE were: epileptic encephalopathy (EE) (58.8%) and focal epilepsy (FE) (29.4%); in LoE, they were FE and multifocal epilepsy (MF) in 42.8%(both types). Between the first and last follow-up, 35.2% of the children with EoE and 48.5% with LoE presented variation in the type of epilepsy; for the first group from FE to EE and for the second from FE to MF in most cases. The predominant antiepileptic drugs at the time of diagnosis in both groups were: valproic acid (54.2%) and vigabatrin (33.3%); at the last assessment they were: levetiracetam (41.6%) and vigabatrin (41.6%). 29.2% and 45.8% of the children received two or more antiepileptic drugs in the first and last assessment, respectively.
Conclusion: In this group of children, EoE was more frequent and debuted mainly as EE. LoE debuted as focal or multifocal, showing a higher percentage of variation between diagnosis and last follow-up. There was a 16.6% increase in children with two or more antiepileptic drugs prescribed in the last follow-up. This five-year analysis evidenced the complexity of epilepsy in children with MZABD, highlighting the need for continuous assessments by an expert group.

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Clinical experience with Brivaracetam IV in emergency situation

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Purpose: To evaluate the seizure control of intravenous brivaracetam in emergency situation setting in clinical practice
Method: Retrospective, multicenter, observational study. Inclusion criteria were: 1. Patients ≥18 year-old; 2. Diagnosed of status epilepticus or seizures with high risk to evolve to status epilepticus; and 3. Use of Intravenous (IV) brivaracetam. Information was extracted from clinical charts and included in a database. Demographic factors, dosage, effectiveness and tolerability were analyzed.
Results: A total of 156 patients were included. The mean age was 57.7 (18-95) years old. At least one comorbidity was reported by 85,6% and 57.1% had a prior diagnosis of epilepsy. Fifty percent presented with structural etiology being the most frequent brain tumors (18.1%) and vascular epilepsy (11.2%). Status epilepticus was diagnosed in 55.3% of the population. Median time from onset of status to IV treatment was 1 hour and median time from the onset of IV treatment to IV brivaracetam was 1 hour. The most frequent treatment line for brivaracetam considering no status vs status was first (41.8%) vs third line (30.1%) and brivaracetam was the last administered antiseizure medication in 80,6% vs 67,5%. Regarding dosages, the mean for initial bolus was 163 mg and 195 mg/day for maintenance. A total of 77,6% of the patients responded to IV brivaracetam (66.3% for status vs 91% for non-status). Seizures did not relapse for 12 hours in 62.8% of the population. The median time to response was 30 minutes. Adverse events were reported by 14.7% of patients. The most frequent were somnolence and fatigue. Adverse events that led to discontinuation were 4.5%. A total of 85.9% patients were discharged with oral brivaracetam.
Conclusion: Intravenous brivaracetam in the emergency setting was effective and tolerability was good in most of the patients. A larger series is needed to confirm these outcomes.

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Web-based decision support system for patient-tailored selection of antiseizure medication in adolescents and adults: an external validation study

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Purpose: Antiseizure medications (ASMs) should be tailored to individual characteristics, including seizure type, age, sex, comorbidities, comedications, drug allergies, and childbearing potential. We previously developed a web-based algorithm for patient-tailored ASM selection to assist health care professionals in prescribing medication using a decision support application (https://epipick.org). In this validation study, we used an independent dataset to assess whether ASMs recommended by the algorithm are associated with better outcomes than ASMs considered less desirable by the algorithm.
Method: Four hundred twenty-five consecutive patients with newly diagnosed epilepsy were followed for at least 1 year after starting an ASM chosen by their physician. Patient characteristics were fed into the algorithm, blinded to the physician's ASM choices and outcome. The algorithm recommended ASMs, ranked in hierarchical groups, with Group 1 ASMs labeled as the best option for that patient. We evaluated retention rates, seizure freedom rates, and adverse effects leading to treatment discontinuation. Survival analysis contrasted outcomes between patients who received favored drugs and those who received lower ranked drugs. Propensity score matching corrected for possible imbalances between the groups.
Results: Antiseizure medications classified by the algorithm as best options had a higher retention rate (79.4% vs. 67.2%, p = 0.005), higher seizure freedom rate (76.0% vs. 61.6%, p = 0.002), and lower rate of discontinuation due to adverse effects (12.0% vs. 29.2%, p < 0.001) than ASMs ranked as less desirable by the algorithm.
Conclusion: Use of the freely available decision support system is associated with improved outcomes. This drug selection application can provide valuable assistance to health care professionals prescribing medication for individuals with epilepsy.

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Extensive pharmacokinetic variability of topiramate in women of childbearing age

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Purpose: Topiramate is an antiseizure medication (ASM) which is increasingly used in women with epilepsy, often as an alternative to valproic acid. Recent studies demonstrate an increased risk of neurocognitive developmental effects in the offspring also of topiramate, with doses from 100 mg/day. The purpose was to investigate pharmacokinetic variability of topiramate in women of childbearing age with epilepsy to elucidate the unpredictable relationship between the dosages used and the exposure in the body in the individual woman and thus consequently, in the fetus.

Method: Retrospective quantitative data from the therapeutic drug monitoring (TDM) database at the Section for Clinical Pharmacology, National Centre for Epilepsy, Norway, were used. Data were collected from women of childbearing age, 14-46 years, who were treated with topiramate during 2020-22.
Results: TDM data from 231 female patients were included, 631 serum concentration measurements (1-17 per patient). Mean age was 31 years and weight 72 kg (given in 32% of the cases). Mean dose was 238 mg/day (median 200 mg), and mean serum concentration 20 µmol/L (median 18) (reference range 6-30 µmol/L). Only 37 measurements (from 23 patients) had doses of <100 mg/day (6%). The interindividual pharmacokinetic variability was extensive, as illustrated by a 13-fold variability in concentration/dose ratios (0.022 to 0.28 µmol/L/mg). The most common dose of 200 mg/day showed serum concentrations in the range of 5-35 µmol/L. Linear regression demonstrated moderate, statistically significant linear correlation between dose and concentration (r^2=0.55) (p<<0.001). The most common comedications were lamotrigine (n=67), levetiracetam (n=53), and valproate (n=45).
Conclusion: This TDM-study of topiramate revealed extensive interindividual pharmacokinetic variability of topiramate in women of childbearing age. The present results call for close follow-up, including the use of TDM to aid decision-making and reduce potential harmful effects.

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Minimum effective sodium valproate dose in genetic generalized epilepsies

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Purpose: Sodium valproate (VPA) is the most effective antiseizure medication (ASM) in genetic generalized epilepsies (GGEs). However, the frequent adverse effects and the high risk inflicted on the exposed offspring make it imperative to search for the lowest daily VPA dose able to control seizures for most patients. In the more recently published series, the value of <1000 mg was the most adopted. This study aims to provide a cutoff VPA value below which a given daily dose can be considered as a low dose in patients with GGEs.
Method: This retrospective, observational cohort study included patients with clinical and electroencephalographic diagnoses of GGEs based on the ILAE criteria. Patients were followed up for at least two years using VPA in mono or polytherapy. Clinical data, VPA dose, and associated ASMs were analyzed. Adverse effects and use during pregnancy were also evaluated. We related seizure control to VPA doses through uni and multivariate statistical analyses.
Results: From 225 patients, 169 (75%) had good seizure control, with most (60%) in monotherapy**.** The cutoff daily VPA dose capable of distinguishing these patients from those without seizure control was up to 1000 mg (p=0.006) in univariate, and up to 700 mg, in the multivariate analyses. For patients in polytherapy, the cutoff was up to 1750 mg and 1800 mg in uni and multivariate analyses, respectively.

Conclusion: The lowest daily VPA dose in monotherapy able to control seizures for most GGEs patients was up to 700 mg, a value that can be used as a low dose criterion in studies assessing the therapeutic VPA ranges. Patients using higher VPA doses or in polytherapy present a lower probability of seizure control.

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Patient self-collected vs nurse-collected fingerprick volumetric absorptive microsampling for antiseizure medication therapeutic monitoring

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Purpose: Volumetric absorptive microsampling (VAMS - Mitra®, Neoteryx) is increasingly proposed as a clinically practical and reliable sampling methodology for therapeutic drug monitoring (TDM). The study aimed to establish the feasibility of patient self-collected VAMS as a practical tool for TDM of antiseizure medication (ASM)[1]. Patient self-collected and nurse-collected VAMS were compared. Plasma ASMs concentrations from venous blood were used as the reference standard to compare blood concentrations found in VAMS.
Method: Epileptic patients on chronic steady-state ASMs were enrolled for this prospective single-centre study. Morning venous and capillary blood by VAMS were collected by nurses1. Afterwards, patients performed VAMS collection by themselves. Blood and plasma analyses were analyzed by ultra-high liquid chromatography-mass spectrometry (UHPLC-MS/MS)2,3,4. ASMs blood concentrations from nurse-collected VAMS were compared to plasma concentrations. A cross-validation study compared ASMs concentrations obtained by nurse-collected *versus* patient-self-collected VAMS samples.
Results: 301 patients (173 females, mean ±SD age 44±16 years), treated with several ASMs (n=13), were enrolled, providing a total of 456 ASMs concentration measurements. VAMS intra-assay and inter-assay reproducibility analyses showed accuracy and precision ≤15%. Samples were stable after seven days of storage at room temperature. A linear correlation between plasma and blood nurse-collected VAMS concentration was performed. Results showed heterogeneous correlation depending on the analytes (R2 ranging from 0.4 to 0.9; $p<0.001$). A cross-validation study between nurse-collected *vs* patient self-collected VAMS showed a bias within ±20% for more than 67% of intrasubject ASMs determinations.
Conclusion: To our knowledge, this is the first study considering the real-world application of patient self-collected VAMS for ASMs TDM. Furthermore, concentration from self-collected VAMS has proved comparable with those from nurse-collected, demonstrating that patient sampling does not introduce variability in quantification results. This VAMS-based method could be considered helpful for TDM, giving a reasonable basis for future at-home VAMS applications.

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Pharmacokinetic variability of cannabidiol in clinical practice

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Purpose: Cannabidiol (CBD) (Epidyolex) is a new antiseizure medication (ASM) used in rare and severe epileptic syndromes. CBD has numerous pharmacokinetic challenges, including low and variable absorption, high protein binding, and enzyme inhibition. The purpose was to investigate pharmacokinetic variability of CBD and its metabolites to elucidate relationships between doses and measured serum concentrations.
Method: Data on serum concentrations of all ASMs, CBD and metabolites 7-OH-CBD (pharmacologically active) and 7-COOH-CBD were collected during 2022 to January 2023. Serum concentration measurements were performed at Section for Clinical Pharmacology, National Centre for Epilepsy, and Dept of Forensic Medicine, Oslo University Hospital. The study was approved by the Regional Ethics Committee.
Results: Data from 33 patients were included, 88 serum concentration measurements (1-8 per patient). Mean age was 23 (range 4-55) years. Mean CBD dose was 425 mg/day (range 20-700 mg/day), mean CBD serum concentration 0.18 mmol/L (range 0.05-0.38 mmol/L) (reference range 0.15-0.45 mmol/L), 7-OH-CBD 0.099 mmol/L (range 0.023-0.20 mmol/L) and 7-COOH-CBD 7.67 mmol/L (range 1.20-20.8 mmol/L). The interindividual pharmacokinetic variability was extensive; 11-fold variation in concentration/dose-ratio of CBD (0.0001 to 0.0012 mmol/L/mg), and 25-fold in concentration-ratio of 7-OH-CBD/CBD (0.06 to 0.46 mmol/L). Intraindividual variability in C/D-ratio was up to 3-fold. Linear regression demonstrated moderate, significant linear correlation between dose and concentration (r^2=0.28) ($p<0.05$). Twenty different ASMs were in use, most commonly clobazam (n=30) and valproate (n=22), and 5 used stiripentol. Concentration ratios of clobazam/desmethyl-clobazam increased significantly by 68% (11.6 to 19.5) ($p<0.05$), pointing to CBD-mediated enzyme inhibition. Unbound valproate concentrations were measured in nine patients but was unchanged, indicating no displacement interaction.
Conclusion: This TDM-study revealed extensive interindividual pharmacokinetic variability of CBD in patients with severe and refractory epilepsy. The present results demonstrate a need for close follow-up and use of TDM to give an optimal and individualized treatment with CBD.

Searching for Safer and More Effective Medications in the Management of Seizure Disorders: A 5-HT2C Superagonist

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Purpose: A ligand eliciting a greater magnitude of response than the endogenous agonist is classified as a superagonist (i.e., higher receptor output signaling). LP352, in development for treatment of Developmental and Epileptic Encephalopathies, is a potent and selective 5-HT2C receptor agonist specifically designed for higher 5-HT2C receptor selectivity versus 5-HT2A and 5-HT2B relative to known serotonergic agonists (e.g., fenfluramine and lorcaserin). The objective of this study was to determine if LP352 exhibits superagonist properties.
Method: *Human 5-HT2C DMR Assays.* Dynamic mass redistribution (DMR) assays were performed using HEK293 cells expressing the human 5-HT2C receptor. Cells were plated in 384-well Corning Epic® plates and incubated overnight in serum-free media. Serially diluted test compounds were applied and DMR responses recorded on a Corning Epic BT reader. Data were analyzed by measuring the change in the DMR response from baseline at a time-point that produced a maximal response – typically 30-60 minutes. *Rat Choroid Plexus Epithelial Cell Assays.* Primary rat choroid plexus epithelial cells, known to express high levels of 5-HT2C, were harvested and cultured for 24 or 48 hours. Cells were plated in DMR assay plates or white, 96-well plates for use in classical inositol phosphate (IP) accumulation assays using [^{3}H]myo-inositol. DMR assays were performed in the same manner as the HEK293 assays.
Results: As the concentration of LP352 increased, its maximal cellular response exceeded that elicited by both lorcaserin and the endogenous ligand, serotonin. In both IP accumulation and DMR assays performed using primary rat choroid plexus epithelial cells, maximal LP352-induced cellular responses exceeded those of serotonin, consistent with classification as a superagonist at 5-HT2C receptors.
Conclusion: LP352 is a 5-HT2C specific superagonist. Further clinical studies should be undertaken to determine if this highly targeted superagonism translates to safety and/or efficacy advantages in relevant disorders.

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Cenobamate as early adjunctive treatment in refractory focal-onset seizures: a cohort study

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Purpose: Cenobamate (CNB) is a new antiseizure medication (ASM) to treat refractory ep-

ilepsy. Data on its use as an early adjunctive treatment are not available yet and clinicians frequently consider CNB to be an ASM of a later choice. We investigared effecacy and safety of cenobamat as early adjunctive treatment in refractory focal-onset seizures.
Method: Study population were patients with refractory focal-onset seizures who were initiated with CNB after they failed to no more than 3 lifetime ASMs, including all prior and concomitant ASM. These patients were matched (1:2) by sex, age and seizure frequency to controls who were initiated with any other ASM than CNB. All participants participated in the Mainz Epilepsy Registry (MAINZ-EPIREG). We evaluated the retention rate after 12 months of CNB and each new adjunctive ASM in the control group. In addition, seizure freedom and response rate (reduction of seizure frequency by ≥50% from baseline) after 12 months were estimated.
Results: We included 231 patients aged 44.4±15.8 years. Of these, 33.3% (N=77) were on CNB, 19.0% (N=44) on valproate (VPA), 17.3% (N=40) on lacosamid (LCS), 16.4% (N=38) on levetiracetam (LEV), 13.9% (N=32) on topiramate (TPM). The highest retention rate after 12 years since the beginn of the early adjunctive therapy was obsereved on CNB (92.2%), compared to LCS (80.0%), LEV (73.3%), VPA (68.2%), or TPM (62.5%) ($p<0.05$). Seizure freedom and response rate were also the best on CNB (19.5% and 71.4%, correspondingly) as compared to other ASMs (8.3% and 52.5%, correspondingly $p<0.05$). No major differences between in adverse events between CNB and other ASMs were observed.
Conclusion: Our study provides preliminary evidence that CNB is an effective and safe ASM in the early adjunctive treatment in refractory focal-onset seizures. This data should motivate further randomised controlled studies to replicate this finding.

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The PACIFIC Study: A Phase 1b/2a Study to Investigate the Safety, Tolerability, Pharmacology, and Exploratory Efficacy of LP352 in Subjects With Developmental and Epileptic Encephalopathies

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Purpose: The developmental and epileptic encephalopathies (DEE) are rare neurodevelopmental disorders characterized by often intractable early-onset seizures and associated with electroencephalographic (EEG) abnormalities and developmental delay/regression. These disorders vary in etiology, seizure type, EEG patterns, cognitive deficits, and prognosis. To date, trials in DEE have focused on specific syndromes (e.g., Lennox-Gastaut Syndrome), even though most anti-seizure medicines are likely effective in broader patient populations. Here, we present a novel trial design focusing more broadly on DEEs using LP352, a potent and highly selective 5-HT2C receptor superagonist.
Method: The PACIFIC study is a double-blind, randomized, placebo-controlled, parallel-group, phase 1b/2a study to assess the safety, tolerability, pharmacology, and exploratory efficacy of

LP352 in patients with DEE. The study consists of three parts: Part 1, a 15-day randomization and up-titration period; Part 2, a 60-day maintenance period; and Part 3, a down-titration/taper period of up to 15 days. Participants are aged 12 to 65, with a diagnosis of DEE (including syndromal [Dravet Syndrome, Lennox-Gastaut Syndrome] and non-syndromal), who have treatment-resistant countable motor seizures while on stable anti-seizure medication treatment. Inclusion criteria for participants with non-syndromal DEE include the onset of unprovoked seizures by age 5, developmental delay, combined focal and generalized seizure types or multiple generalized seizure types, slow or disorganized EEG background, and no diagnosis of idiopathic generalized seizures.
Results: This study will provide insight into the safety, tolerability, and PK/PD profile of LP352 in a variety of DEE patients, while providing proof of concept for a more generalizable, non-syndrome-based DEE trial.
Conclusion: LP352 has the potential to be the most highly selective 5-HT2C-targeted therapy to reduce seizures in DEE. The data from this study should inform future clinical trials on the appropriate and effective dosing for efficacy measures including underlying seizure types and DEEs.

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Efficacy and Tolerability of Perampanel in Pediatric Patients with Dravet Syndrome: Single Institution Retrospective Study

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Purpose: To assess the efficacy and tolerability of perampanel in patients with Dravet syndrome.
Method: The medical records at King Faisal Specialist Hospital & Research Centre (KFSHRC) of all pediatric patients were retrospectively reviewed. Patients with Dravet syndrome and using perampanel were included in the study. The collected data included their demographic characteristics, seizure pattern and perampanel description, and laboratory and radio-image findings.
Results: The study included 18 pediatric patients with equal gender distribution. Mean age was 9.94 ± 3.670. Mean age of perampanel initiation was 7.67 ± 3.865. Majority of patients had 2 types of seizures (61.1%) followed by three types (22.2%). Generalized tonic-clonic was the most frequently reported type of seizure (100%). Out of the 18 patients, 13 patients underwent genetic analysis revealing a *de novo* pathogenic variant. Twelve had the variant in *SCN1A* gene ,while one in *PCDH19* gene. The mean efficacy of perampanel was 29.17 ± 29.368, with only one patient with 100% efficacy to perampanel. The duration of perampanel in weeks was 37.22 ± 48.350. Patients aged 8 years and younger presented with higher efficacy (p-value = 0.037) ,and the number of drug side effects were positively correlated with the

drug efficacy.
Conclusion: This study presented evidence of promising therapeutic potentials for perampanel among some patients with Dravet syndrome, with data supporting the value of this treatment. Additional studies are required to confirm and verify the current findings.

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Treatment of Drug-Resistant Infantile Spasms with CER-0001, a Ketogenic Agent: Preliminary Results

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Purpose: A pilot study to evaluate CER-0001, also known as tricaprilin, for the drug-resistant treatment of Infantile Spasms. Initial results of the first 6 enrolled subjects are presented; the study is to enroll 10 subjects. Infantile spasms (IS) is a disorder characterized by epileptic spasms, developmental regression, and hypsarrhythmia. Ketogenic diets have been used in the management of drug resistant epilepsies, especially including IS. CER-0001 is an orally administered, liquid, ketogenic agent, and may offer the same benefits in terms of spasm reduction as a ketogenic diet, whilst allowing the continuation of the current source of nutrition.
Method: This is an open-label study of CER-0001 in children with IS, aged 3-24 months, who have failed treatment with vigabatrin and prednisolone (or ACTH). Subjects have a 24h vEEG recording to establish eligibility and baseline spasm/seizure frequency. CER-0001 is up-titrated over 5-14 days. Subjects with clinical benefit at the end of the titration period receive maintenance treatment for 7 days, and undergo a repeat 24h vEEG. Current formula and medications are left unchanged.
Results: Random sampling of blood β-hydroxybutyrate levels indicates all 6 subjects were in ketosis (βHB levels above 0.5mM) by the end of the titration phase and in the maintenance phase. In three out of six subjects, a response (≥50% reduction in number and duration of epileptic spasms) was seen on the vEEG. One serious adverse event of 'aspiration' was considered related to treatment.
Conclusion: Initial results of CER-0001 for the treatment of infantile spasms from a prospective trial warrant continued investigation.

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A review on role of metformin as a potential drug for epilepsy treatment and modulation of epileptogenesis

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Purpose: Available anti-seizure medications (ASMs) target the symptomatology of the disease

rather than disease/epileptogenesis modifying actions, leading to critical concerns of drug resistance and seizure recurrence in epilepsy management. So, drug repurposing is evolving as a paradigm change in quest for novel epilepsy treatment strategy. Metformin, a well-known anti-diabetic drug has shown multiple pieces of evidence of its potential antiepileptic and anti-epileptogenic action.
This review elucidated the various mechanisms and evidence about the beneficial role of metformin in seizure control and modulation of epileptogenesis.
Method: Articles pertaining to both preclinical and clinical evidence involving metformin in epilepsy and special conditions like tuberous sclerosis were summarised. The putative mechanisms of metformin relevant to epileptogenesis modulation are also discussed.
Results: This review found the efficacy of metformin in different seizure models including genetic knockout model, chemical induced, and kindling models. Only one clinical study in tuberous sclerosis has shown a reduction in seizure frequency and tumor volume compared to placebo. The suggested mechanisms of metformin relevant to epileptogenesis modulation mainly encompass AMP activation, m TOR inhibition, protection against blood-brain-barrier disruption, inhibition of neuronal apoptosis, and reduction of oxidative stress. In addition to seizure protection, metformin has a potential role in attenuating adverse effects associated with epilepsy and ASMs such as cognition and memory impairment.
Conclusion: Metformin has shown promising utility in epilepsy management and epileptogenesis modulation. The evidence in this review substantiates the need for a robust clinical trial to explore the efficacy and safety of metformin in persons with epilepsy.

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Utilization of a pharmacokinetic (PK) model for STK-001, an antisense oligonucleotide (ASO), in patients with Dravet Syndrome (DS) to predict pharmacologically active doses in clinic

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Purpose: DS is a severe and progressive genetic epilepsy; most cases are due to a pathogenic mutation in the *SCN1A* gene leading to haploinsufficiency of $Na_v1.1$ protein. STK-001, an ASO, is being developed for DS treatment. STK-001 is designed to upregulate $Na_v1.1$ brain protein expression by leveraging the wild-type copy of *SCN1A* to restore physiological $Na_v1.1$ levels, thereby potentially reducing both seizure frequency (SF) and non-seizure comorbidities. Non-clinical PK studies identified STK-001 brain levels that elicit a 2-fold increase in $Na_v1.1$, which is the desired pharmacology in patients. Here we provide simulation data in DS to predict dosage for pharmacologically active STK-001 brain levels.
Method: A semi-mechanistic population PK model was developed based on STK-001 concentration collected in 141 non-human primates (NHP) after single or multiple intrathecal (IT) administrations. Observed time-concentration profiles in CSF, plasma, spinal cord and brain tissues were adequately described using a 15-compartment model with parallel linear and

saturable elimination from the plasma compartment, and lag time for dose input. NHP PK model was physiologically scaled to pediatric DS population of three age groups (2-<8, 8-<13 and 13-≤18 years). Human PK model was further adapted using observed CSF, CSF transfer rates, plasma exposure, brain volumes, age, and weight from 49 patients after single or multiple STK-001 administration (10-45mg) in phase 1/2a and open labeled extension studies.
Results: Brain STK-001 levels were extrapolated based on CSF trough concentrations and were mostly within 95th CI of model simulations. Median simulated and extrapolated human brain concentrations in most patients following 3 monthly doses (20-30mg) are within the minimum pharmacologically active concentration range determined in preclinical studies.
Conclusion: There was good agreement between model predictions and observed plasma and CSF concentrations. This supports the selection of dosing and regimen that allows maintenance of pharmacologically active STK-001 levels in brain across three age groups.

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Learning from a European consortium for epilepsy trials (ECET)

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Purpose: Present and share our experience in building ECET, an innovative project led by Epilepsy Alliance Europe (EAE) and the Rare and Complex Epilepsies European Reference Network (ERN EpiCARE).
Method: The annual number of new epilepsy patients in Europe is estimated to be 130,000 children and adolescents; 96,000 in adults 20–64yrs; 85,000 in the elderly. More than 30% of patients with epilepsy develop a rare or complex form. Trials on antiseizure medications, the development of targeted therapies and prospective studies in epilepsy-surgery or cognition are either poorly implemented or lacking. Differently designed clinical trials, better adapted to the specific unmet needs remain a priority. Learning from the past, several defaults (e.g methodological; underpowered; selection of centres with limited expertise in targeted populations; feasibility questionnaires not adapted to the field) can be rapidly remedied.
ECET was launched by European investigators with recognized expertise in trial designs and epilepsy care, aiming to improve the quality of European collaborative trials, in both adults and children. Established under EAE, a non-profit organization under the auspices of the ILAE and the IBE, the Consortium guarantees a meaningful representation of professionals, patient advocates and other stakeholders.
Results: During the first year since it was launched, 76 members joined ECET, either affiliated to EpiCARE or representing non-EU countries. A Memorandum of Understanding with the

US Epilepsy Consortium is in place. Together with the EpiCARE Working Group for clinical trials and targeted therapies seven Task Forces are in place. Constructive partnerships were established between Academia, Pharma, Clinical Research Organizations (CROs) and patient organizations.
Conclusion: Targeted surveys were launched and ECET contributed to the scientific review of trial designs and site selections. By sharing our first results and a critical review of our experience we invite those with expertise or interest in epilepsy trials to join ECET's efforts.

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Drug development readiness for epilepsy syndromes

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Purpose: Increasing competition in the epilepsy space and technological advances in genetic treatments have led to an increased focus on epilepsy syndromes as the target for clinical trials in epilepsy. Epilepsy syndromes are orphan indications and offer several advantages to drug developers, including better defined patient populations and market exclusivity. But developing treatments for epilepsy syndromes also comes with unique challenges such as lack of regulatory precedent or high competition for a reduced number of patients. This abstract describes an analysis of drug development readiness for epilepsy syndromes to better understand the opportunities and challenges for each of these indications.
Method: This study focused on the ten epilepsy syndromes that have received the most attention and investment by drug developers to date. These include CDKL5 Deficiency Disorder, Dravet syndrome (SCN1A), KCNQ2, Lennox-Gastaut Syndrome, PCDH19, SCN2A, SCN8A, STXBP1, SYNGAP1 and Tuberous Sclerosis Complex. For each, we analyzed the level of drug development readiness along two axis: (1) Clinical and Regulatory Feasibility, and (2) Market and Competition.
Results: When analyzed for drug development readiness, the ten disorders covered in this study cluster in three groups: (1) syndromes where clinical development is de-risked and competition is high; (2) syndromes where clinical development has not yet been de-risked and competition is still low; and (3) syndromes where clinical development is de-risked and competition is still low. In addition to clustering epilepsy syndromes by drug development readiness, this analysis also highlights areas of improvement for each of the syndromes to accelerate and de-risk the development of novel therapeutics.
Conclusion: The results of this study provide insights into the different opportunities and challenges for developing new treatments for rare epilepsy syndromes, as well as recommendations that can be incorporated into planning the development of novel therapeutics.

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Use of ketogenic diet in patients with *SCN8A*-related epilepsy: report on two clinical cases

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Purpose: To describe ketogenic diet (KD) efficacy in two patients with drug-resistant epilepsy suffering from *SCN8A*-related developmental and epileptic encephalopathy.
Method: We performed a retrospective evaluation collecting electroclinical data.
Results: Patient 1 presented at age 4 months with subsequent seizures characterised by generalized hypertonus, desaturation, cyanosis and staring. EEG showed theta-delta activity and isolated bilateral fronto-temporal delta-waves and spikes. Psychomotor development remained normal until 10 months of age when, after status epilepticus, he lost previously-acquired developmental milestones and EEG deteriorated. He developed drug-resistant epilepsy, despite therapeutic approaches with phenytoin, nitrazepam, oxcarbazepine, lamotrigine and carbamazepine, the latter at supramaximal dosage according to literature. At age 15 months KD was added and seizures' duration and frequency progressively lowered in accordance with KD ratio increase. At last follow-up, he has been seizure-free for six months and EEG showed physiologic sleep pattern.
Patient 2 presented at 4 months with subsequent seizures characterised by generalised tonic-clonic jerks, loss of consciousness and desaturation, followed by high frequency seizures. He showed severe developmental delay, with wax and wane in his ability according to seizures' frequency. EEG showed diffuse, unresponsive delta-band activity and no differentiation between wakefulness and sleep. Focal evolving to generalised tonic-clonic seizures persisted with multiple-daily frequency. Several antiseizures medication were tried: phenobarbital, valproic acid, topiramate, and oxcarbazepine, the latter at supramaximal dosage. At the age of 27 months KD was introduced and marked reduction in seizure frequency was recorded, with up to two weeks seizure-freedom periods. The last EEG showed diffused theta activity with sporadic epileptic discharges.
Conclusion: Evidence of KD's efficacy in patients with *SCN8A*-related epilepsy was reported in few anecdotal cases (Gardella et al. *Neurology*, *91*(12), E1112–E1124), however the precise action mechanism and long-term efficacy are not yet known. In this study we describe two cases in which KD showed a significant positive electro-clinical effect.

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Experience in the use of cannabidiol in a South Sardinian epilepsy center

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Purpose: We present data about the first 9 adult subjects treated with Cannabidiol at the Epilepsy Center of Policlinico Universitario of Monserrato, Cagliari, Italy between September 2020 and December 2022.
Method: We selected patients suffering from drug-resistant epilepsy, with a diagnosis of Len-

nox-Gastaut syndrome (n=8) or Dravet syndrome (n=1).
Results: Cannabidiol was titrated on a weight basis with steps of 2.5 mg/kg every 2 weeks up to a dosage of 15 to 20 mg/kg/day. Patients were taking between 2 and 4 concomitant anti-seizure medications (ASM); 3 patients were treated with Vagus Nerve Stimulation; 1 patient underwent epilepsy surgery. Among them, the most common side effect (n=2, 22.2%) was drowsiness; in one case this necessitated discontinuation of the drug. Monitoring of laboratory tests showed no alterations, even in a patient with a history of liver dysfunction. One patient, on concomitant therapy with Clobazam and Valproic Acid, presented a serum overdose of VPA. 1 patient was seizure free (11.1%), 2 patients presented a seizure reduction between 50 and 75% (22.2%), 4 patients presented a seizure reduction between 25 and 50% (44.4%), 2 patients between 0 and 25% (22.2%).
Conclusion: Anti-seizure effects of Cannabidiol have been hypothesized for several years; it was approved by the FDA and EMA and is effective for seizure control in patients with Dravet syndrome, Lennox-Gastaut syndrome, and Complex Tuberous Sclerosis. Its mechanism of action is not completely known but its metabolism leads it to interact with several ASM, particularly Clobazam. The most common side effects are hepatocellular damage, sedation, suicidal ideation, and hypersensitivity. The combination of cannabidiol and clobazam leads to an increased anti-seizure effect at the cost, however, of increased risk of adverse effects, which must be carefully evaluated and monitored in the individual patient. Close clinical and laboratory monitoring allows Cannabidiol to be used even in patients with hepatic comorbidities.

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Initial experience with cenobamate as a treatment option for patients with drug-resistant focal epilepsy in a reference centre for epilepsy surgery

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Purpose: Despite recent therapeutic advances in epilepsy, 25% of patients continue to have drug-resistant epilepsy, limiting the benefit of anti seizure medications (ASM).
Cenobamate (CNB) is a recently approved ASM. Acting as a sodium channel blocker and GABA receptor modulator, it becomes an option for the treatment of focal onset epilepsy. It has shown a good impact in reducing seizures for drug-resistant epilepsy patients on clinical trials, providing a new therapeutic alternative that improves the quality of life of these patients.
We aim to evaluate the clinical response to this AMS in a real-life setting.
Method: Retrospective analysis of effectiveness, safety and tolerability of cenobamate with focal refractory epilepsy in a referal center for surgical evaluation. Data is collected through medical active charts.
Results: Cenobamate has been started in 64 patients (33 women, 31 men), suffered from highly refractory epilepsy, with a mean age of 38.78 years. 17 patients have 3 months of follow up and 26 have more than 6 months with CNB. They were receiving an average of 4.5

MACs. Up to 37,5% of them are implanted with vagus nerve stimulator. We found a >50% reduction in seizures in 31 patients (51,16%) at 3 months and 18 patients (58,3%) at 6 months, including patients with 90% seizure reduction. Drowsiness (50%) and dizziness (26.6%) were identified as the most frequent adverse effects, which mostly improved after dose adjustment of the remaining MACs (phenobarbital, clobazam, sodium channel blockers). In six patients the drug was withdrawn due to adverse effects, in three of them of them despite low doses.
Conclusion: In a highly refractory sample of patients, cenobamate has shown significant efficacy in reducing seizures.
Drug tolerability can be optimized by adjusting the dose of the rest of the concomitant ASM.

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Drug discovery and repurposing to find a treatment for Lafora disease

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Purpose: Lafora disease (LD) is a rare recessively inherited disorder characterized by progressive myoclonic epilepsy and cognitive and motor deterioration. Symptoms occur between 10 and 20 years of age and life expectancy is about 10 years. LD is caused by mutations in *EPM2A* and *EPM2B* genes encoding for laforin and malin, two proteins involved in glycogen metabolism. Indeed, laforin or malin dysfunctions cause glycogen accumulation in the brain, leading to rapid neurodegeneration. There is currently no therapy able to limit glycogen accumulation and halt disease progression. Available symptomatic approaches include antiseizure medications (ASM), ketogenic diet, trehalose, metformin (Mitra et al., Rev Neurol 2022). Enzyme- and oligonucleotide-based therapies are still under investigation. Thus, new pharmacological targets and drugs need to be identified to ensure patients an early and effective treatment. The purpose of this study is the repurposing of commercial drugs by using computational strategies to speed-up the identification of new therapies. Three possible brain targets, i.e., human glycogen synthase (hGYS1) and glucose transporters (GLUT1/3) have been selected to identify putative ligands among commercial drugs through docking based-virtual screening.
Method: Molecular docking studies were thus employed to investigate an *in house* curated database of 35 ASM towards hGYS1 and GLUT1/3 crystal structures. Docking simulations were performed using Grid-based Ligand Docking with Energetics which is part of the Schrodinger Suite.
Results: The preliminary *in silico* analysis revealed a potential binding capability towards hGYS1 and GLUT1/3 binding sites for piracetam, levetiracetam, ethosuximide, zonisamid. As such, these drugs might be able to reduce glucose access and glycogen synthesis in the brain.

Experimental assays are ongoing to confirm these results.
Conclusion: We have identified four ASM showing potential additional mechanisms of action that could be relevant in LD therapy. By limiting glucose accumulation in LD patients, these drugs could become ASM of choice in LD treatment.

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Long-term efficacy and safety of cannabidiol in the treatment of drug-resistant epilepsy: a systematic review

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Purpose: To investigate the long-term efficacy and safety of cannabidiol in treatment of drug-resistant epilepsy.
Method: We searched three databases: Medline (via PubMed), Embase (via Ovid), and CENTRAL. A total of 50 records were included, including 47 studies and 3 extension studies. Efficacy effect sizes included response rates (> 50% reduction in seizure frequency from baseline) and free seizure rates at 12, 24, 48, 72, 96, and 144 weeks. Safety effect sizes included the rates of adverse events and serious adverse events. Subgroup analysis was performed by the age of 14 years. Random effect model and intention-to-treat set were used for data analysis. Both fixed-effects models and prer-protocol set were used as sensitivity analyses. Revman 5.4 was used for Meta-analysis.
Results: **Efficacy:** The response rates and 95% confidence interval of intention-to-treat set of random effects model were 0.41 (0.36, 0.45), 0.38 (0.33, 0.43) and 0.37 (0.30, 0.44), 0.27 (0.17, 0.37) and 0.22 (0.14, 0.30) and 0.38 (0.23, 0.53) respectively. And free seizure rates were 0.04 (0.03, 0.05), 0.04 (0.03, 0.05) and 0.03 (0.02, 0.05), 0.03 (0.02, 0.03) and 0.02 (0.01, 0.03) and 0.04 (0.01, 0.06) respectively.
Safety: The rates of adverse events were 0.72 (0.61, 0.83), 0.62 (0.42, 0.81) and 0.60 (0.41, 0.79), 0.35 (0.14, 0.56) and 0.83 (0.75, 0.90) and 0.96 (0.94, 0.99) respectively. And the rates of serious adverse events at 12, 24, 48, 96 and 144 weeks were 0.15 (0.09, 0.21), 0.23 (0.14, 0.31) and 0.10 (0.06, 0.15), 0.31 (0.24, 0.38) and 0.40 (0.35, 0.45) respectively.
Conclusion: Response rates and free seizure rates remained stable from 12 to 144 weeks. The rates of adverse events and serious adverse events tended to increase with the increase of use time. There were time-efficacy and time-safety interactions. The benefit-risk ratio needs to be considered comprehensively in treatment of drug-resistant epilepsy .

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Highly purified cannabidiol for children with Lennox Gastaut Syndrome with differ-

ent aetiology: effect on seizures and comorbidities

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Purpose: To assess the real-world effectiveness and safety/tolerability of Highly purified cannabidiol (Epidyolex) when used as add-on in patients with Lennox-Gastaur Syndrome.
Method: Highly purified cannabidiol (Epidyolex) has been approved by European Medicine Agency in 2019 and by Agenzia Italiana del farmaco in 2021 to treat patients from 2 years with Lennox-Gastaut Syndrome (LGS). We analyse 6 Italian patients (mean age:10.3 years, range:7-17 years), included in a preliminary study, treated with Epidyolex in add-on (mean follow up:13 months, range:6-24 months). 6/6 had LGS diagnosis (based on seizures types, EEG pattern, cognitive dysfunction), due to genetic aetiology in 4/6 (KCNQ2, GNAO-1, CACN1E and inv-dup 15 tetrasomy), metabolic/genetic in 1/6 and unknown in the remaining patient. All patients underwent genetic and neuroimaging investigations, if not previously performed. Intellectual disability, behavioural abnormalities and movement disorders were reported in 6/6. At the baseline, seizure frequency (generalized tonic-clonic, tonic, myoclonic seizures, spasms and atypical absences), considering 6 months before cannabidiol initiation, EEG, blood test results, neurological evaluation with clinical description of MDs were reported. Patients continued concomitant treatment (clobazam in add-on for 6/6). A titration scheme was used: 5mg/kg to 20mg/Kg/day. CGI scales were performed (after 6 months and one year).
Results: Epidyolex was well tolerated in 6/6. Efficacy on seizures was reported for 6/6 (seizures reduction ≥ 75% for 3/6, ≥ 50% for 3/6). Alertness, emotional functioning and behaviour improved in 4/6. Movement disorder patterns consisted of dyskinesia/dystonia in 4/6 children, dyskinesia/stereotypies in 2/6. MDs significantly decreased in 4/6 patients.
Conclusion: Further studies are needed to confirm effect of Epidyolex on seizure and comorbidities in patients with LGS according to the aetiologies. Our results suggested that cannabidiol was safety and efficacy on seizures control and on the improvement of comorbidities such as behavioural problems and movement disorders in most children of our series.

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Clinical use of fenfluramine in adults with *SCN1A*-related disorders

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Purpose: To assess the effect of fenfluramine treatment in a retrospective series of three

patients with intractable *SCN1A*-related epilepsy.
Method: Participants with an *SCN1A* related disorder were treated with Fenfluramine at a starting dose of 0,036, - 0,088mg/kg/day and titrated to effect. The primary outcome measure was reduction of seizure frequency.
Results: Three adult patients with *SCN1A*-related disorders were enrolled in the study age, 24-34. Two patients were diagnosed with Dravet syndrome, and the third patient suffered from a developmental and epileptic encephalopathy due to a gain-of-function variant in *SCN1A.* After 3 months of treatment, the two patients with Dravet syndrome showed a marked decrease in seizure frequency with regard to generalized tonic clonic seizures (GTCS). In contrast, the patient with the *SCN1A* gain-of function variant had no beneficial effect on her epilepsy.
Patient 1: 34-year-old female with Dravet syndrome. Seizure semiology: generalized tonic-clonic (GTCS), and myoclonic seizures. Outcome: seizure reduction from 15 to 3 GTCS per months.
Patient 2: 24- year old female with Dravet syndrome. Seizure semiology: GTCS, myoclonic seizures and abscences. Outcome: Tonic seizures 44-72 (per month) before treatment to 56 – 66 (per month).
Generalized tonic clonic 28-35 (per month) before treatment to 11- 22 (per month).
Patient 3: 25-year-old female with a gain-of-function missense variant in *SCN1A*. Seizure semiology: hemiclonic seizures, series of nocturnal myoclonic seizures and myoclonic status epilepticus. Outcome: lack of effect and adverse events led to treatment cessation.
Conclusion: Three adult patients with *SCN1A* related disorders were treated with fenfluramine. The two patients with Dravet syndrome due to loss-of-function variants in *SCN1A* experienced 80 % and 50 % seizure reduction, respectively, whereas the patient with a *SCN1A* gain-of-function variant had no clinical effect of fenfluramine.

Epidemiology

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Translation and validation of an epilepsy-screening questionnaire in two Ghanaian languages

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Purpose: To validate an epilepsy-screening tool for a household survey under the larger Epilepsy Pathway Innovation in Africa Study (EPInA) in Shai-Osudoku and Ningo-Prampram District of Greater Accra region, Ghana.
Method: A 17-item epilepsy screening questionnaire was developed by modifying validated English language questionnaires. We included questions on convulsive and non-convulsive seizures. Separate multilingual experts forward- and back-translated them to two target languages, Twi and Ga-Dangme. Cases were people with epilepsy attending healthcare facilities where these languages are spoken. The controls were relatives of cases or people attending for other medical conditions. Cases and controls were matched for geographical location and ethnicity. Questions were grouped into stages 1 and 2 for household and case/controls respectively. An affirmative response to any of the seventeen questions amounted to a positive screen.
Results: A total of 100 (50 cases and 50 controls) for Twi and 140 (70 cases and 70 controls) for Ga-Dangme were recruited. The sensitivity and specificity of the questionnaire were: Stage 1; (Twi 98 % and 92%, Ga-Dangme 100% and 80% respectively) and stage 2 (Twi 96% and 94%, Ga-Dangme 98.6% and 85.7% respectively). The two versions reliably indicated epilepsy with positive predictive values of 92.5% and 83.3% for Twi and 83.8% and 87.3% for Ga-Dangme at stages 1 and 2 respectively. The questionnaire reliably excluded epilepsy with negative predictive values of 97.9% and 100% for Twi, 86.0%, and 98.4% for Ga-Dangme respectively.
Conclusion: A validated epilepsy screening questionnaire is now available for the two languages to be used for community-based epilepsy surveys in Ghana.

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Evaluation of doctors' knowledge and attitudes in the field of breath-holding spells

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Purpose: To evaluate the knowledge as well as the scientific attitude of doctors who are implicated in the management of children with BHS.
Method: A cross-sectional study was performed on 280 doctors who reacted to our questionnaire, including pediatric residents, pediatric consultants, pediatric neurology fellows, pediatric neurology consultants, pediatric emergency physicians, and general practitioners. Online questionnaires were posted to all followers of the Neuropsychiatric and pediatric scientific groups, in the El Behira governorate, Egypt during the period from January- April 2019. Doctors in the current study were requested to give their answers to each of the questionnaire items, then answers were collected, tabulated, and statistically analyzed.
Results: We noted that 25.0% of the doctors had high scores, 47.1% had average scores and 27.9% had weak scores regarding knowledge scores. While 97.1% of them had positive scores and 2.9% had negative scores regarding their attitudes toward BHS management. Comparison of the BHS knowledge scores in relation to the general and personal data of the study sub-

jects showed a significant statistical difference in the scores regarding their age, gender, current position, specialty, level of care, and impression about the commonness of the cases of BHS. On the other hand, comparison of the scores that assess the attitude toward BHS management in relation to the general and personal data of the study subjects, showed significant statistical differences in the scores regarding their age, current position, specialty, years in practice, degree of graduation, level of care, impression about the commonness of the cases of BHS, and awareness about BHS management guidelines
Conclusion: there is a wide range of variations regarding BHS knowledge and attitudes toward BHS management among physicians from various disciplines. a considerable number of them require more training on clinical guidelines.

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Study of epilepsy in rural population

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Purpose: This study was aimed to study the profile of rural epileptic patients in Southern India.
Method: This retrospective study was carried out from January 2017 for five years at ABC Hospital Trichy, KM Crescent Hospital Trichy and Dhanalakshmi Srinivasan medical College Hospital, Siruvachur. All the epileptic patients attended the neurology OPD were recorded and analysed.
Results: In five years, 8000 epileptic patients were registered and which were account for 18% of patients among neurological consultations. About 6400 (80%) of the patients were from rural areas. Among them 3840 (60%) were male and 2560
(40 %) were female. Among rural patients 11% were in 0 to 10 years,35% were in 11 to 20 years, 29% were in 21 to 30 years, 13% were in 31 to 40 years and 12 % were above 41 years of age. Regarding treatment with AEDs from the onset of seizure, 10% of patient came within first week,8% of patients came within a month, 20% of patients came with in one year, 16% of the patients came from 1 to 3 years and 46 % of patient came after 3 years.
Among all, 9% of the patients got medications with first seizure. Among seizure types, 44 % partial seizure, 24% secondary generalization, 26% GTCS, 5 % myoclonic seizure and 1% had absence seizure.
As treatment , 33% were on phenytoin sodium, 11% on carbamazepine,13% on sodium valproate and 10% on phenobarbitone , 10% on oxcarbamezepine , 20% on levetiracetam and 3% were on lamotrigine.
Conclusion: Epilepsy is one of the common neurological problem among the patients from rural area . About 46% of the rural epileptic patients came after 3 years of onset of seizure for treatment. Nearly 57% of the rural epileptic patients were on older AEDS. 86% rural epileptic patients were on poly therapy with AEDS.

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Patient journeys: a tool to raise awareness on the evolution, common needs, and critical issues of patients with rare and complex epilepsies

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Purpose: Share with epilepsy carers the characteristics of "Patient Journeys" (PJ).
Method: PJs are tools developed by the European Reference Networks (ERNs) and patient representatives' (ePAG). They reflect consensual experiences of patients with rare diseases; identify gaps and areas for improvement; summarize steps of care pathways; elements considered positively by those affected. When compared they highlight common needs and relevant differences. They allow clinicians, not experts in rare diseases, to recognise new critical signs as early as possible and promptly refer the patient to centres of expertise.
Results: ERN EpiCARE patient representatives already worked on the development of five PJs, (https://epi-care.eu/patient-and-caregiver-leaflets/), in collaboration with their patient community and medical experts. PJs summarize both state-of-the-art, based on scientific literature critical reviewing, and patients' experiences and needs. Patients/carers and family doctors can jointly identify gaps in care services, adapt care pathways, diagnostic procedures and treatments, discuss what outcomes and challenges are relevant at different stages.

Such information being regularly updated, helps EpiCARE experts in identifying earlier, needs for future research and knowledge generation. Other collectively produced documentation (Patient and Caregiver leaflets; Emergency protocols), freely accessible to non-experts, families and the public, supplement this project.

Understanding the needs and specificities of people affected by complex, drug-resistant epilepsies, the natural evolution of its rare forms are fundamental to a meaningful societal integration of the patients, to the support of clinical research and the necessity for a sound collaboration with the medical community.
Conclusion: "Patient Journeys " and "pathways" are working documents, regularly updated. Produced by patient advocates and medical experts they represent one of the main benefits the patients' community can expect from EpiCARE. With more than 150 rare forms of epilepsy we make a plea to both experts in the field and patient associations for an active contribution to this ambitious project.

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Incidence of psychogenic non-epileptic seizures in a defined geographical area: a prospective cohort study

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Purpose: Psychogenic non-epileptic seizures (PNES) are an increasingly recognised phenomenon whereby the signs and symptoms of epilepsy may be experienced without the underlying physiological abnormalities. Epidemiological studies investigating prevalence and incidence of PNES are relatively uncommon but are essential to provide better estimates of the true occurrence of PNES which is essential for health-care planning. This study aimed to assess the incidence of PNES in a cohort of patients who presented with potential seizures during 2017 in a defined geographical location and to reassess this rate at three-years to account for changed diagnoses.
Method: The studied cohort had been previously identified and included patients presenting with a possible seizure during 2017. These were subdivided into newly-diagnosed epilepsy patients, seizure mimics, provoked seizures and first seizure with low chance of recurrence. For this study, we looked at the seizure mimics and specifically those who had been labelled with a possible or definite diagnosis of PNES. Incidence rates were calculated for the initial time of data collection and at the three year follow-up point.
Results: There were 1264 people ultimately studied for the 2017 incidence study with 510 diagnosed with a seizure mimic and 40 of these categorised as definite or possible non-epileptic seizures. Thirty (75%) were over 18 and 10 (25%) were under 18 years of age. The initial crude incidence rate of possible PNES cases in the 2017 study was 7.37 per 100,000 people. The new incidence rate at three years was 7.55 per 100,000 people.
Conclusion: This study found a higher incidence of PNES compared to previous investigations which is likely reflective of the 'all-comer' nature and comprehensive ascertainment methods utilised in the original 2017 study. Although further incidence studies are essential to inform health-care planning regarding PNES, we believe this inclusive study adds to the collective knowledge currently available.

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Three-year seizure outcomes in a cohort of patients with newly diagnosed epilepsy

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Purpose: Epilepsy is a common, global and often chronic neurological disorder with potentially far-reaching consequences for its sufferers and their families. This study aimed to investigate the three-year seizure outcomes in an established cohort of patients diagnosed with epilepsy in the year 2017 in order to evaluate the early natural history of epilepsy.
Method: The studied cohort had been previously identified and included patients diagnosed

with epilepsy during 2017. Data collection involved interrogation of the patient's charts, clinic letters and electronic hospital databases for up-to-date information on seizure frequency, anti-seizure medications and drug resistance. Additionally, some of the participants were contacted to partake in a phone interview for further detail. Data was analysed using SPSS software.
Results: There were 334 definite and probable patients with newly diagnosed epilepsy defined in the 2017 cohort. From these, 236 were followed-up at three years. There were 107 (45.34%) females and 129 (54.66%) males. There were 164 (69.5%) adults and 72 (30.5%) children. Overall, prognosis was good with the majority of people on a single ASM with no reported side-effects, who were linked in with neurology services and had no major seizure-related injuries or hospitalisations. A large proportion (69.92%) reported being seizure-free for over one year with a smaller number becoming drug-refractory (9.32%) and the remainder experiencing intermittent seizures.
Conclusion: The results of this data favour an overall good prognosis for epilepsy in terms of seizure outcomes such as serious injuries, recurrent hospitalisations, ASM side-effects and drug resistance with a high rate of seizure freedom seen among the studied cohort.

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Three and five-year mortality outcomes in a cohort of patients with newly diagnosed epilepsy

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Purpose: Premature mortality is a significant concern in the epilepsy population, particularly in the early years of diagnosis. Deaths in the setting of epilepsy arise both directly and indirectly. This study investigated the three-and five-year mortality outcomes in an established 'all-comer' cohort of patients newly diagnosed with epilepsy in the year 2017.
Method: The studied cohort had been previously identified and included patients diagnosed with epilepsy during 2017. Information on the number and cause of deaths was obtained through a search on the hospital database and the electronic database for Irish reported deaths with additional review of patient charts and electronic records. Further information was gathered or confirmed through the General Registry Office and primary care physicians.
Results: Out of 334 potential participants, 72 people (21.5%) had died three years after initial diagnosis with an additional 13 deaths by five years. The 65+ age group were primarily affected with infections and malignancies representing the major causes of death. Standardised mortality ratios were calculated as 2.01 at three years and 2.02 at five years.
Conclusion: Despite the often favourable prognosis in epilepsy, premature mortality remains a significant concern, especially in those who have been newly-diagnosed. This study particularly demonstrates the increased risk of early mortality in the older age groups who have additional co-morbidities and an overall increased predisposition for frailty-related morbidity and mortality.

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Effects of the new definition of epilepsy (ILAE 2014) - a prospective study

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Purpose: In 2014, the ILAE proposed a new definition of epilepsy whose practical implications in terms of incidence, treatment, and outcomes have not yet been studied.
Thus, it remains unclear whether this change in definition will result in more frequent diagnoses of epilepsy, and whether this will influence recurrence rates.
Method: From March 2018 to March 2020, all adult patients admitted to our department with a first epileptic seizure were asked to participate. Demographic and clinical data were collected at baseline and at 6 and 12 months. Descriptive statistics are reported as absolute numbers with percentages, means ± (SD), or medians ± median absolute deviations. To investigate factors affecting seizure recurrence, a binary logistic regression was performed with second seizure (yes/no) as the dependent variable and age, use of ASM, IED in the EEG, and structural lesions on imaging. All analyses were calculated using SPSS version 27 software (IBM, 2020).
Results: Data were collected from 235 adult patients (41.7% female). 146 patients were diagnosed with epilepsy directly with the onset of the first seizure (PWE), and 89 patients were discharged with a diagnosis of the first seizure. 33.6% of PWE had interictal epileptiform discharges on EEG. Potential epileptogenic lesions on imaging were detected in 49.3% of PWE. At the first follow-up, 143 patients (77.3%) were seizure-free, and 89 of the PWE were seizure free (70.6%). At the second follow-up, 129 of the 160 patients (80.6%) were seizure-free. 77 of the PWE were seizure free (72%). The use of ASM decreased (odds ratio = 0.46) the recurrence rate significantly.
Conclusion: The new definition of epilepsy results in a higher frequency of epilepsy diagnosis, followed by higher treatment frequency. The short-term outcome is good (recurrence rate 19.4 % after one year). Reasons are unclear. Thus, further studies are needed to investigate the impact of ASM on long-term outcomes.

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Association between epilepsy and subsequent years of working life – a Danish population-based cohort study

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Purpose: Epilepsy can affect workforce participation in numerous ways. In this study, we aim to estimate the association between epilepsy and working years lost, defined as the number of years not actively working or enrolled in an educational program.
Method: In this population-based cohort study, we included all individuals aged 18-65 years in the Danish Civil Registration System from Jan 1, 1995 to Dec 31, 2018. Information on epilepsy and labour market characteristics was obtained from national registers. Follow-up started at age 18 years, immigration to Denmark, or on Jan 1, 1995, whichever came later; and ended at age 65 years (age of retirement in Denmark), death, emigration from Denmark, disability pension, voluntary early retirement or Dec 31, 2020, whichever came earlier. The main outcome was working years lost for persons diagnosed with epilepsy as well as for the general population of same age and sex.
Results: In total, 5.7 million individuals (48.7% women) were followed for 91.0 million person-years, of which 76,790 (1.4%) were diagnosed with epilepsy. During follow-up, 1,199,800 (21.1%) individuals left the labour market prematurely before age 65 years; 388,630 (6.8%) due to disability pension, 663,630 (11.7%) due to voluntary early retirement, and 147,540 (2.6%) due to premature mortality. Compared with individuals without epilepsy, a larger proportion of those diagnosed with epilepsy left the labour market prematurely due to being granted a disability pension (23.7% vs 6.6%), or death (7.8% vs 2.5%) and a smaller proportion retired through a voluntary early retirement (6.3% vs 11.7%). Numbers were rounded to nearest 10 due to confidentiality.
Conclusion: Epilepsy may have a substantial impact on workforce participation, and using recently developed methods [Plana-Ripoll O. et al. Lancet Psychiatry 2023;10.1;30-39], we will estimate excess working years lost in persons with epilepsy, decomposed into periods of unemployment, sick leave, disability pension, voluntary early retirement or death.

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Predictors of crisis management in genetic generalized epilepsies in a South American hospital

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Purpose: Identify factors predictors with crisis management in patients with generalized genetic epilepsies.
Method: Case-control study with a cohort of patients greater than 14 years old diagnosed

with generalized genetic epilepsy, and 12-month follow-up, excluded patients with a diagnosis of epileptic encephalopathy. Sociodemographic, clinical characteristics and survey characteristics were evaluated for the evaluation of relapse factors; bivariate and multivariate analyzes were performed using binary logistic regression.
Results: Between 2018, 59 patients who met the selection criteria were evaluated. The factors predictors with epileptic seizure control were: medical comorbidities (OR: 5.48, 95% CI: 2.95-13.42, P<.001), health plan assurance (OR: 4.1, 95% CI: 1.60- 8.55, P.004), individual attitudes (OR: 4.5, 95% CI: 2.54-6.85, P<.001) and the number of seizures on admission to the epilepsy program (OR: 0.89, 95% CI 0.78-0.99, P.003); There was no association with a psychiatric, family or psychoactive substance use history.
Conclusion: It is demonstrated that 45% of the crisis control of this cohort of patients can be explained by the factors found, so that if they are impacted and a comprehensive intervention is performed, there is a direct impact on crisis control and thus in the long-term forecast.

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The influence of patient's age at first epileptic seizure on seizure recurrence: a preliminary analysis

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Purpose: To evaluate whether the patient's age at first epileptic seizure affects the risk of seizure recurrence.
Method: This is a preliminary retrospective analysis of a large database of all patients accessing the emergency department of our hospital for epileptic seizures from 2001 to 2021. We included data on a randomly chosen subset of patients with a first-ever seizure. We stratified patients according to their age at first seizure: <15 years, 15-65 years, and >65 years. We compared the risk of a first seizure recurrence in different time intervals (30 days, 90 days, 6 months, 1 year after the first seizure) with a Kaplan-Meier survival analysis.
Results: We included data on 377 patients (135 with seizure recurrence, 35.8%). Overall, the risk of seizure recurrence after a first-ever epileptic seizure was highest in patients aged >65 years and lowest in those aged 15-65 years. A significant difference in risk of seizure recurrence was observed in the 30 days (p=0.017), 90 days (p=0.014), and 6 months (p=0.009) after the first seizure; the difference was not significant at 1 year (p=0.09).
Conclusion: Our preliminary analysis shows that the patient's age at first seizure affects the risk of recurrence up to 6 months. Overall, in this timeframe the risk appears highest in patients aged >65 years and lowest in those aged 15-65 years. Future analyses will investigate further the role of age in seizure recurrence, considering the difference between acute symptomatic and unprovoked seizures, seizure etiology, and other prognostic factors.

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A prospective population-based study of the incidence of status epilepticus according to the new definition: a longitudinal comparison

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Purpose: Status epilepticus (SE) represents one of the most common neurological emergencies. Until 2008, the definition of SE included an epileptic seizure lasting more than 30 minutes or a series of seizures without complete recovery of consciousness. Based on that definition, the incidence was given with 17,1/100 000 for Germany (Knake et al. Epilepsie;2001;42:714-718.). Now consistent treatment of generalized SE should be started after five minutes of clinical seizure activity (Lowenstein et al. Epilepsie; 1999;40:3-8; DGN since 2001). Therefore, the objective of this study was to collect the first epidemiological data after the change of definition in the same region that was used to define the incidence in Germany in 2001.
Method: According to the study in 2001, a prospective population-based study was conducted from 2018 to 2020. 181 adult patients were included who lived in the postal code area 35xxx, which can be considered representative for Germany, as well as a selected urban area "A", due to its population structure and suffered a seizure of at least 5 minutes duration or repeated seizures without recovery. A follow-up was performed approximately 30 days after discharge.
Results: The age-adjusted annual incidence of SE in urban area A was 28.1/100 000 (vs. 14/100 000 in 2001). It was higher in men than in women (30.9 vs. 25.5/100,000) and higher in persons > 60 years than < 60 (62.9 vs. 13.6/100,000). The 30-day lethality in area A was 5.6%. The overall 30-day lethality in the 35xxx zip code area was 11.6%.
Conclusion: This study provides the first epidemiological data on the new definition of SE in Germany. Compared to the incidence using the old definition in 2001, there is an increase in the incidence in adults. It is likely that the change in definition plays an important role in the increasing incidence.

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Social status and health care utilisation before the diagnosis of idiopathic generalized epilepsies

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Purpose: To investigate social status and health care utilisation at the time of diagnosis in patients with Idiopathic Generalized Epilepsies (IGE) in Denmark.
Method: We extracted a cohort of 3448 Danish IGE patients from the National Patient Register based on ICD10-codes in the period 2005-2018 together with 34480 age-, sex- and geography-matched controls from the Danish Civil Registration System (DCRS). We compared registry data on family income level, affiliation with the labour market, civil status, criminal offences, placements outside of the family home and contacts to the health care system at time of epilepsy diagnosis. A cohort of 402 well characterized IGE patients from Funen, Denmark, matched with 4020 randomly selected age-, sex- and geography-matched controls via the DCRS served as validation cohort.
Results: In Danish IGE patients, register data on social status measured by family income, civil status, affiliation with the labour market, number of children and placements outside of the family home, indicated worse social status of patients before IGE diagnosis as compared to matched population controls. Further, patients had more somatic as well as psychiatric comorbidity at epilepsy diagnosis as compared to matched population controls. In the validation cohort, differences in social status showed similar tendencies, but did not reach statistical significance. It confirmed however, that IGE patients have more frequent contact to their general practitioner ($p=0.04$), more hospitalisations ($p<0.0001$) and have a higher number of both somatic diagnoses ($p<0.0001$) and psychiatric diagnoses ($p<0.0001$) at time of epilepsy diagnosis than matched population controls.
Conclusion: Register data indicate lower socioeconomic status and higher somatic and psychiatric comorbidity in IGE patients already at diagnosis. These data support the concept of IGE being a neurodevelopmental disease with symptoms prior to epilepsy onset.

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The incidence of sudden unexpected death in epilepsy (SUDEP) in Ireland

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Purpose: To determine the incidence of SUDEP in the Republic of Ireland.
Method: The role of the coroner in Ireland is to enquire into the circumstances of sudden and unexplained deaths. The Irish coronial system is such that we could reasonably expect the majority of SUDEP cases to be referred to the coroner.
The Health Research Board(HRB) has an established mechanism in place for accessing data held by the coroners in the Republic of Ireland. Research nurses from the HRB examined all coroner service files for 2019 and identified those with a possible diagnosis of epilepsy. Information on the subjects' cause of death, epilepsy and medical history was extracted from the

post-mortem record and any other available records.
This data was then further analysed to identify cases which could be confidently labelled as SUDEP. An up to date incidence of SUDEP in the Irish Republic was determined based on an epilepsy prevalence of 1%.
Results: Thirty -one cases were felt to be consistent with definite SUDEP, 19 males and 12 females with an age range of 9 to 81 years and a median age of 44 years. All deaths occurred within the home, the majority within the bedroom. A single death was witnessed. SUDEP was listed as the cause of death on the death certificate in 18 of these cases. Based on this data the SUDEP incidence in the Irish Republic in 2019 is 1:1580 across all age groups.
Conclusion: This is the only study of SUDEP incidence in the Republic of Ireland and the rate calculated is in keeping with the literature. This study shows the usefulness of coronial data and the expertise of the HRB in gathering information on epilepsy deaths in the Republic of Ireland.

Financial support was provided by Epilepsy Ireland, the Irish Institute of Clinical Neuroscience and Jazz Pharmaceuticals.

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The top ten epilepsy research priorities: a UK priority setting partnership

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Purpose: Despite being one of the most prevalent, serious neurological conditions, epilepsy received only 0.3% of the total £4.8 billion UK Government funding spent on health-related research in 2018. To evidence the need for greater investment, a James Lind Alliance (JLA) Priority Setting Partnership (PSP) was conducted.
Method: The UK Epilepsy PSP adopted JLA methodology, forming a steering group to represent the UK's epilepsy community: people affected by epilepsy, epilepsy healthcare profes-

sionals and UK patient organisations. The steering group developed a survey to collect the research priorities of the epilepsy community, which were then categorised and translated into distinct researchable questions. Questions previously answered by research were removed during an evidence checking process, and unanswered questions formed the basis of a second shortlisting survey. Shortlisted questions were then reviewed and discussed at the UK Epilepsy PSP Workshop, where the final Top Ten questions for epilepsy research were agreed.
Results: Collectively, the UK Epilepsy PSP surveys received nearly 5,000 individual responses. The highest proportion of responses were from people with epilepsy, followed by parents of children with epilepsy. In the first survey, 541 responses were from healthcare professionals. The most frequently reported research priorities included antiseizure medication, SUDEP and epilepsy in women. The final Top Ten research questions were published in October 2022. Several priorities shared commonalities with the research recommendations of the WHO IGAP.
Conclusion: Funded and led by Epilepsy Research UK, the UK Epilepsy PSP is a once-in-a-generation, national consensus collating the views of the UK epilepsy community, to generate the evidence needed to influence government and institutional funders to ensure research into epilepsy receives an equitable share of research funding. Importantly, funded research will focus on the priorities of those most affected. We will provide an update on the ongoing work to action these research priorities and their impact so far.

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Tuberous sclerosis complex (TSC) in the Republic of Ireland - making the invisible visible

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Purpose: To identify the number of patients with a diagnosis of Tuberous Sclerosis Complex (TSC) attending neurological services in The Republic of Ireland (ROI) and assess the level of compliance with the United Kingdom (UK), TSC Consensus guidelines within these services.
Method: Patients with a diagnosis of TSC attending twelve adult and paediatric neurological centres in the ROI, were identified through the National Epilepsy Electronic Patient Record and secondary chart review. Clinical audits measured the care of 83 of the 135 identified patients. Care was benchmarked against UK, TSC clinical guidelines. The audits included 46 questions under the following headings:patient characteristics, genetics,central nervous system, kidney, lung, heart, eyes, skin, liver and pancreas. Data was anonymised and analysed in

Trinity College Dublin.
Results: 135 TSC patients attending twelve neurological centres were identified. Adults (n= 67) paediatric (n= 68). The care of 83 patients was audited, (n=63 ≥18yrs.) and (n=20 < 18 yrs.). Information on specialist services and treatments, including the use of mTOR inhibitors, recommended for the management of TSC was available. Many baseline tests were completed, especially in the paediatric services. However, recommended services were not always available within all hospitals and referrals to other sites were required. SUDEP was only discussed in 15.6% of adult and 25% paediatric cases. Neuropsychology evaluation appears inadequate in adult services. The (TAND) assessment tool was not used in either adult or paediatric services. Renal MRI (baseline) was performed in 45.7% of adults and 55% of children. Genetic results were available for 49% of adults and 85% of children.
Conclusion: The number of TSC patients attending neurology services is lower than expected (n=135). Specialist services and treatments for TSC are available. The UK, TSC consensus guidelines baseline recommendations are broadly adhered to, especially in paediatirc services. Increased coordination of care could benefit disease management in adult services.

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Identification of drug resistant epilepsy in the Danish national patient register

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Purpose: The main purposes of this study was to to identify drug resistant epilepsy (DRE) and its correlates in the validated cohort from the Danish National Patient Registry (DNPR), based on criteria set out by The International League Against Epilepsy (ILAE).
Method: We identified all individuals who were registered with a first diagnosis of epilepsy or seizures in the Region of Central Jutland, Denmark from 2010-2019. We reviewed electronic records on a random sample and validated the epilepsy diagnosis according to ILAE criteria. We determined each epilepsy patient's drug response status as of the last visit (at a mean of 5.3 years of follow-up), as: DRE, drug-responsive epilepsy, or undefined drug responsiveness. We performed logistic regression analyses to identify factors correlated with risk of DRE.
Results: Of 20,723 patients with a first diagnosis of epilepsy or seizures in the Region of Central Jutland from 2010-2019, we reviewed the medical records of 1,687 patients (46% females, mean age at onset = 42.4 years). Of these, 1,077 (64%) were registered with epilepsy in the DNPR. The epilepsy diagnosis was confirmed in 838 cases, providing a positive predictive value (PPV) of 79% (95% CI: 75-80%). Of 740 patients with confirmed incident epilepsy and ≥ 1 year of follow-up, 103 (14%) fulfilled the definition of DRE, 476 (64%) were drug responsive, and 161 (22%) had undefined responsiveness. In multivariable logistic regression analysis, early age at onset, cognitive impairment, and a history of status epilepticus were

factors independently associated with DRE.
Conclusion: In the validated cohort identified from the Danish National Patient Registry, 14% fulfilled ILAE criteria of drug resistant epilepsy. Early age at onset, cognitive impairment, and a history of status epilepticus correlated with drug resistance.

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Is revascularization in ischemic stroke associated with risk of post-stroke epilepsy?

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Purpose: Revascularisation therapies of acute ischemic stroke; thrombolysis and thrombectomy, have revolutionised the treatment of acute ischemic stroke, as they have improved recovery and survival after stroke. However, studies of the effect of revascularisation treatments on the risk of post-stroke epilepsy has been scarce and results conflicting.
Method: In the Danish Stroke Registry, we identified all patients diagnosed with a first ischemic stroke between January 1, 2011, and December 16, 2018, who did not have a history of epilepsy. We followed patients from 14 days after stroke until diagnosis of epilepsy, death, immigration, or December 31, 2018, whichever came first. We used the Danish National Patient Register to identify persons diagnosed with epilepsy, and the Danish Civil Registration System to assess vital status and link individual information across registries. Cox regression models were used to estimate the hazard ratio of epilepsy associated with revascularisation adjusted for stroke severity, cortical symptoms, sex, age and Charlson Co-morbidity index.
Results: We included 54,430 ischemic stroke patients, of whom 45,410 (83.4%) received no revascularisation therapy, 7,250 (13.3%) were treated with thrombolysis, 640 (1.2%) were treated with thrombectomy and 1,130 (2.1%) were treated with both thrombolysis and thrombectomy.
Compared to non-revascularized patients, adjusted hazard ratios for epilepsy were 0.71 (95% CI: 0.56-0.90) for patients treated with thrombolysis and thrombectomy, 0.74 (95% CI: 0.64-0.85) for patients treated with thrombolysis, and 0.89 (95% CI: 0.65-1.23) for patients treated with thrombectomy.
Conclusion: In adults with ischemic stroke, revascularisation therapies were associated with lower risk of post-stroke epilepsy compared to no revascularisation therapy.

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Absence status epilepsy – case report

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Purpose: Absence status epilepticus (ASE) is a prolonged absence seizure - the patient is alert but only partially responsive for even several hours. It is usually provoked by withdrawal of antiepileptic drug or by usage of inaccurate medication. Here we present a case of a patient with recurrent AS without these provoking factors.
Method: Here, we report a case of a 31-year-old woman with ASE along with EEG samples.
Results: The patient was a 31-year-old woman diagnosed with juvenile absence epilepsy at the age of 11. She has been treated with valproate. Absence seizures occurred every 2-3 months, they were usually provoked by sleep deprivation. At the age of 27 valproate was withdrawn and treatment with lamotrigine was started (300mg per day), with good seizure control. After a year, during upper inspiratory tract infection, the first generalized tonic clonic seizure occurred. The EEG revealed normal background and fragments of generalized spike-and-wave and polyspike-and-wave 3 Hz discharges.
In the last 2 years typical absence seizures occurred once for a few months, although prolonged episodes of orientation disorders, psychomotor slowdown and illogical contact appeared. Symptoms resolved after diazepam administration. The patient was hospitalized 3 times in our hospital although we were not able to register EEG during these symptoms. The serum level was normal. We have suspected recurring absence status epilepticus. One of the episodes has been provoked by infection, for the others we were unable to determine the provoking factor. Finally, during the next episode, EEG was performed and we have registered almost continuous, generalised spike-and-wave and polyspike-and-wave discharges with amplitude up to 150µV.
Conclusion: In this patient we have diagnosed absence status epilepsy. This is a newly defined syndrome characterized by recurrent ASE without provoking factors. Status epilepticus could be the only manifestation of the disease, in some patients typical absence seizures occur.

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Two and half decades of community directed treatment with Ivermectin for onchocerciasis control in Mahenge, an area endemic for epilepsy: where do we stand?

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Purpose: Epidemiological evidence suggests that onchocerciasis can directly or indirectly induce epilepsy, although the exact mechanism is not yet understood. Therefore, the study investigated the prevalence of onchocerciasis and epilepsy following the long-term use of ivermectin to control onchocerciasis in the Mahenge area.
Method: The study was conducted in four and 34 villages in 2017 and 2021, respectively. Door-to-door household visits were conducted to enumerate the population for sampling, followed by clinical screening for suspected epilepsy cases using standardized questionnaires and neurological confirmation of their status. Additionally, children aged 6- 10 years were examined for onchocerciasis antibodies using the Ov16 rapid test. Data were summarized using descriptive statics, Chi-square, and correlation tests.
Results: A total of 5160 individuals (median age 18.5 years, 47.8% male) were registered in 2017 and 58,000 individuals in 2021. In 2017, 513 children were screened for onchocerciasis, of which 20.7% were positive, with the prevalence being high in two rural villages compared to two sub-urban (38.4 vs 3.7%, p<0.001). In 2021, the Ov16 prevalence was 12.3% (494/4004), with rural villages most affected. The self-reported uptake of ivermectin was 74.4% in 2017 and 80.4% in 2021. The overall prevalence of epilepsy in 2017 was 20.4 per 1000 persons, with the rural village having a higher prevalence (28.4 vs 13.2 per 1000, p<0.001). From 2017-2021, the onchocerciasis prevalence in the two rural villages decreased from 38.4%-24.3%, p<0.001, while in the two- sub-urban villages, there was no significant different change between 2017 and 2021 (3.7% vs. 5.3%, p=0.528). A high correlation between the prevalence of epilepsy and onchocerciasis was observed in all surveys.
Conclusion: Onchocerciasis and epilepsy are still common despite ivermectin usage for two and half decades, with the most affected communities being those in rural areas. Hence the need for community interventions to complement ivermectin distribution.

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Management of pediatric status epilepticus in 11 Italian hospitals: 12-years of real-world clinical practice

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Purpose: The Italian Paediatric Status Epilepticus (IPSE) Group encompasses eleven Italian, hospital-based centres with Pediatric Intensive Care Units, aiming to collect and analyse real-world data on diagnosis and treatment of SE. Knowledge deriving from these results will be applied to establish diagnostic procedures and treatment recommendations applicable at all levels from rescue ambulances to emergency hospital rooms and wards.
Method: Retrospective observational study collecting clinical data of SE occurring in the last 12 years. The following variables were analysed: number of patients and number of SEs, age at SE the onset, presence of new onset SE, aetiology, refractoriness, adherence of therapy to international treatment protocols, use of midazolam (MDZ) over the years.
Results: We collected data on 1372 SE from 1063 patients. Median age of onset of the first SE was 3 years. Onset within the first two years was observed in 512 patients (37.7%). New onset SE occurred in 52.3% of patients. Main aetiologies were genetic, both known and presumed, in 453 patients (58.3%) and structural in 223 patients (20.9%). There were 807 (62%) non-refractory SE, 471 (36%) were instead refractory and 30 (2.3%) were super refractory. In 864 SE (63%), treatment followed national and international guidelines while in 508 patients (37%) treatment was non-adherent. Use of MDZ increased in the last 5 years from 72% to 76%. This difference was significant for MDZ in continuous infusion, in non-anaesthetic dosage, which was effective in 71% of cases. In the last 5 years, refractoriness was also significantly reduced from 42% to 36% of SEs.
Conclusion: SE is relatively common in children, often manifesting in infancy, aetiology is genetic in > 50% of patients. About a third of SE are refractory yet our data show that this rate is decreasing in accordance with the more frequent use of continuous infusion of MDZ at non-anaesthetic doses.

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Prediction of idiopathic epilepsy in India by artificial neural network using different global burden of disease predictors

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Purpose: Epilepsy, one of the most common neurological disorders with 50 million population affected globally, has unknown cause in 50% cases. Rest 50% cases have secondary origin and association with disorders pertaining to health or environment. Though, several studies

have analyzed the clinical aspects and molecular mechanisms of epilepsy; there is scarcity of studies establishing the strength of association of epilepsy with other causative problems i.e. prediction of epilepsy using some relevant predictors.
Method: In this study, we have used an Artificial Neural Network (ANN) for predicting idiopathic epilepsy using adverse drug reactions (ADR), anxiety, congenital birth defects (CBD), depression, encephalitis, endocrine-metabolic-blood-immune disorders (EMBI), environmental heat and cold exposure (EHC), meningitis, nutritional deficiency, poisoning, substance abuse disorders (SAD) as predictors. The data for these parameters were collected from Global Burden of Diseases database from the Institute for Health Metrics and Evaluation as percentage contribution by each of these towards death and injury year wise from 1990-2019 for India. Data is divided into training (1990-2012) and testing (2013-2019). Then, the data is pre-processed using min-max normalization method and backpropagation algorithm is applied for ANN training.
Results: Over the years data, idiopathic epilepsy is having strong positive correlation with anxiety, EHC, EMBI, and poisoning (r=0.9271, 0.7598, 0.7338, 0.7319, respectively) and negative correlation with CBD, encephalitis, meningitis, SAD (r= -0.8707, -0.7014, -0.7854, -0.7807, respectively). We have tested the epilepsy predictive accuracy using predictors individually and in combination. As per goodness-of-fit (R^2) measure the prediction performance follows the order of poisoning >depression >encephalitis >nutrition deficiency >EHC >CBD >meningitis >EMBI >anxiety >SAD >ADR. While using all the predictors, the performance has improved (R^2=0.87).
Conclusion: The predictive performance of poisoning is better followed by depression and other predictors for idiopathic epilepsy in India. However, combination of these aforesaid predictors has performed well as per the Global Burden of Diseases outcomes.

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A retrospective non-interventional study evaluating the prevalence of rare diseases associated with epilepsy at three epilepsy centres

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Purpose: Although epilepsy is a common disease, many patients suffer from so-called rare diseases, defined by a prevalence of less than 1/2,000. Diagnosing a rare disease in the individual patient may have prognostic and therapeutic implications but “rare diseases” are also important with regard to further research. Our centres have a long tradition and focus specifically at patients with seizure disorders including persons with a wide range of disabilities.
Method: Retrospective, cross-sectional survey at three major European epilepsy centres. We evaluated the prevalence of rare diseases associated with epilepsy from data of all in- and out-patients during week 40 of the year of 2020 in the centres. Assessment included demo-

graphic variables medical history, and outcome parameters.
Results: We evaluated 504 patients (236 females). 44% (n=222) suffered from a rare disease according to Orphanet. 32% (n = 162) had a structural, 19% (n = 94) a genetic or presumably genetic, 3% (n = 13) an inflammatory/infectious, 1% (n = 4) a metabolic and 2% (n = 10) an autoimmune epilepsy. Almost all patients showed co-morbidities such as infantile cerebral palsy, hemiparesis, ataxia, intellectual deficits or behavioural disorders. The most common rare diseases were mesial temporal epilepsy with hippocampal sclerosis, Dravet syndrome and Tuberous Sclerosis Complex.
Conclusion: A significant portion of patients of traditional epilepsy centres suffer from rare and complex diseases associated with or resulting in epilepsy. Many of these patients might require a more specific therapeutic approach than hitherto available. Hence, it is crucial to identify those rare diseases and the comorbidities associated with them, in order to be able to provide the patients with appropriate medical care. Traditional epilepsy centres which are not necessarily associated with universities care for a huge number of patients with rare diseases and can contribute to research in this field.

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Epileptic encephalopathies: collection of electroclinical aspects, findings in neuroimaging and etiological diagnosis in a cohort of patients seen in our refractory epilepsy unit

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Purpose: New diagnostic techniques have revolutionized the neurodevelopomental and epileptic encephalopathies, enabling reliable identification of etiologic specific syndromes. However, at least a relevant proportion of patients - estimated as 50% - remain undiagnosed. We aim to evaluate if advances in diagnostic testing are reflected in a real-life setting
Method: Retrospective analysis of patients seen at the epilepsy clinic for the last 1 year with drug-resistant epilepsy (DRE) onset before 12 years old and neurodevelopmental alterations. We excluded patients with neurodevelopmental delay associated to other disorders or if there were insufficient data for an adequate evaluation. We evaluated the performance of prolonged EEG monitoring (at least 24 hours), epilepsy protocol MRI and genetic testing. Most of patients had a previous karyotype study from the early childhood.
Results: N=67 patients (29 men, 38 women) were included, with a current mean age of 35.22 years old.
All of them have prolonged eeg monitoring (including sleep). Epilepsy protocol MRI were performed in N=45(67%). Genetic tests were requested, including N=25(37%) exome studies. With these tests performed, N=32(48%) reached a definitive etiological diagnosis, highlighting N=19(28%) with genetic etiology (15 of them of monogenic origin) and N=13(19%)

with structural etiology (ulegyria and FCD type 1 as the most frequent diseases). N=35(52%) didn't reach a definitive etiological diagnosis, including N=13(19%) with results still pending. N=4(5.9%) present DEE due to unknown etiology despite a complete study.
Patients have an average of 3.84 ASM. Over time, N=17(26%) are well controlled.
Conclusion: Despite new advances in diagnostic techniques, there is still a percentage of undiagnosed patients.
Whole exome sequencing is particularly relevant in order to identify monogenic mutations associated to epileptic encephalopathy that may not be identified with other techniques.
Given the fact that these patients present poor control of seizures, it is important to refine the diagnosis in order to optimize the therapeutic approach.

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Application of machine learning for idiopathic epilepsy prediction in India based on environmental heat and cold exposure

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Purpose: With the advent of frequent heat waves and winter storms, environmental heat and cold exposure (EHC) is becoming a major determinant for chronic neurological disorders including epilepsy. In a tropical country like India, epilepsy (prevalence 0.47% of population) needs timely and accurate prediction as it directly affects the livelihood of millions of people. This study has analysed predictability of idiopathic epilepsy using EHC through different machine learning techniques.
Method: The year-wise data pertaining to percentage contribution of idiopathic epilepsy and EHC for causing death and injury in India from 1990-2019 were collected from Global Burden of Diseases database from Institute for Health Metrics and Evaluation. Dataset was partitioned into training and testing in the ratio 75:25. After data pre-processing, different machine learning techniques such as Artificial Neural Network (ANN), Decorrelated Neural Network Ensembles (DNNE) and deep Long Short-Term Memory Neural Network (LSTM-NN) were used after tuning certain network parameters for predicting idiopathic epilepsy using EHC as a predictor.
Results: The correlation analysis showed that idiopathic epilepsy has strong positive association with EHC (correlation coefficient 0.7598). This proposed model for predictability of idiopathic epilepsy using EHC as a predictor is efficient for predicting the idiopathic epilepsy statistically as verification is done on an independent test dataset (2013-2019). Among the machine learning techniques, higher goodness of fit measure was achieved by deep LSTM-NN (0.9511) as compared to ANN (0.4169) and DNNE (0.8926).
Conclusion: It was found that deep LSTM network has better capability to learn the intrinsic data if the network is tuned properly using predictor like EHC. This machine learning technique can be used as a prediction tool to predict the prevalence of idiopathic epilepsy in

India.

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Prevalence of interictal epileptiform discharges in a routine short term out-patient EEG: a study from a teritiary care centre in South India

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Purpose: EEG is the cornerstone in diagnosing epilepsy. Single routine outpatient 40-minute EEG shows interictal epileptiform discharges (IEDs) between 29% and 55%. The purpose of the study is to determine the prevalence of IEDs in a single 40-minute outpatient EEG.
Method: We performed retrospective analysis of routine outpatient 40-minute EEGs to find the prevalence of IEDs. The EEGs done between January 2018 and December 2022 were analysed. Indication for EEG was epilepsy. The proportions were calculated to the total number of EEGs done during the study period.
Results: Of the 4293 EEGs done during the study period, 994 (23.1%) EEGs showed IEDs. Generalized IEDs diagnostic of idiopathic generalized epilepsy were observed in 298 (6.9%): IEDs suggestive of symptomatic generalized epilepsy in 12 (0.27%). Focal IEDs were observed in 684 (15.9%) EEGs. Of the EEGs with focal IEDs, 285 EEGs showed slow background activity and 372 normal background activity corresponding to the location of IEDs. The lobar distribution of focal IEDs was: temporal in 9.4%, frontal in 2.2%, posterior quadrant 2.5% and hemispheric in 1.1%. In 21 (0.48%) IEDs pattern were diagnostic of Self-limited epilepsy with centrotemporal spikes. Nineteen (0.44%) EEGs showed ictal rhythms: generalized in 1 and focal in 18 EEGs. Seizure semiology and ictal EEG onset concordance was suggestive of temporal lobar onset in 7, frontal lobe onset in 5 and posterior quadrant in 3. Two EEGs showed hemispherical onset. One EEG showed EEG patterns consistent with nonconvulsive status epilepticus. Seizure semiology was suggestive of psychogenic non-epileptic seizures (PNES) with no ictal EEG correlate was observed in 44 (1.02%) patients.
Conclusion: In this study, the prevalence of IEDs, both generalized and focal, was comparable to western series. However, the prevalence of PNES was significantly low (1.02%).

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Idiopathic generalized epilepsy: sociodemographic characteristics and drug resistance

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Purpose: To describe the sociodemographic characteristics, identify the most used drugs and determine the drug resistance and pseudo-drug resistance of patients with idiopathic gener-

alized genetic epilepsy in general and subgroups in our healthcare center.
Method: The database of patients from our institution from 2019 to 2022 was retrospectively reviewed, including patients diagnosed with idiopathic genetic epilepsy.
Results: We obtained a total of 231 patients. The mean age was 13 years, 54.54% male, the mean age of first crisis 12 years (range 7-35 years). The most frequent diagnosis was juvenile myoclonic epilepsy, 108 patients (54.62% men), 63.30% without seizures, and 17 and 5 patients presented pseudo-drug-resistance and drug resistance, respectively. The second most frequent subsyndrome was generalized epilepsy with generalized tonic-clonic seizures only, 76 patients (55% men), 60.5% without crisis, and 11 and 4 patients presented pseudo-drug-resistance and drug resistance, respectively. The childhood absence epilepsy group was of 28 patients (28.58% men), 57.14% without seizures, and 8 and 1 patients presented pseudo-drug-resistance and drug resistance, respectively. The juvenile absence epilepsy group was of 19 patients (47.37% men), 68.42% without seizures, and 2 and 1 patients presented pseudo-drug-resistance and drug resistance, respectively. The mean ages were 12 and 13 years in drug-resistance and responsive patients, respectively. Levetiracetam was the most used drug in juvenile myoclonic epilepsy and generalized epilepsy with only generalized tonic-clonic crisis. Valproic acid was the most widely used drug in juvenile and childhood absence epilepsy.
Conclusion: We observed good response to drug treatment in all groups of idiopathic generalized epilepsy. In most of the cases that continued with seizures, it was due to pseudo-drug resistance. The mean age in drug-resistance patients was lower than in responsive response patients, like previous series. The most used drugs were levetiracetam and valproic acid.

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Epilepsy and Covid-19 correlation, patient follow-up for two years in Regional Hospital Durres, Albania

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Purpose: There are a few potential ways that the SARS-CoV-2 virus may trigger seizures.More present factors are hypoxia in severe covid 19 that can induce anoxic encephalopathy which could trigger seizures, inflammation with an inflammatory reaction and a cytokine storm that can induce hyperexcitability of neurons and potentially result in seizures, particulary in febril patients, infecting cells that line the blood brain-barrier, electrolyte imbalances and emotional stress was seen as trigger seizures.
Method: From 380 patients with covid 19 that are hospitalized at infectious department (resuscitation patients in a very serious condition or intubated) in SRD in period January 2021 and December 2022, 22 patients had epileptic seizures. All patient had the first time this cri-

sis. (13 of them were woman and 9 were men). Middle age of patients was 54.6 years. from the group of patients, 16 of them had a decrease in saturations of 88-91% and had stage III pulmonary involvement. 9 of them medium stage pulmonary involvement.
Results: 9 of the patients had seizures with generalized convulsions, 3 atonic seizures,10 partial seizures,
4 of the patients had seizures again within 2 weeks. In CT, 6 patients had edema and cerebral hypoxia, 14 patients without cerebral changes, 2 patients with frontal and parietal ischemic areas. All patients had a good clinical response. 3 patients repeated the crisis within 6 months and 2 patients repeated the crisis in the 11th and 20th months after infection. All patients were followed up with control EEG for 3 months – 2 years.
Conclusion: 22 patients (6.4% of cases) of our study has epileptic seizure and 5 of them made repeated crises for 2 years period.

Epilepsy and Reproductive Health

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Neonatal outcomes in women with new-onset epilepsy in pregnancy

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Purpose: The aim of this study was to investigate neonatal outcomes in women with new-onset epilepsy during pregnancy (WNOEP).
Method: 112 pregnant women with epilepsy were prospectively evaluated at the Education – Therapeutic Clinic of the Azerbaijan Medical University, in the neurological and maternity departments of the Clinical Medical Center in Baku over a six-year period. Women were regularly followed by a neurologist and obstetrician until the end of pregnancy. To determine the recurrence of seizures during the pregnancy and after delivery, the women were followed up at least once per three months for a one-year period after delivery. Neonatal outcomes for WNOEP were compared with those for 277 healthy women in the control group (without epilepsy and without registering chronic diseases).
Results: Of the 112 pregnant women with epilepsy, 12 (10.7%) had their first seizures during the pregnancy. Medical termination due to frequent seizures was performed in one woman. Nine women underwent cesarean sections. Vaginal delivery was performed in 2 patients. Eleven WNOEP gave birth to 11 babies; 277 women in the control group to 277 babies. The risks of perinatal hypoxia in WNOEP were not increased compared to women with epilepsy before pregnancy (Odds ratio [OR]: OR 2.18; 95% CI 0.61-7.76, respectively), but were significantly higher in infants born to WNOEP when compared with the control group (OR 3.61, 95 % CI 1.06-12.27). We did not find any correlation of fetal hypoxia to antiepileptic drug use and number of prior pregnancies in WNOEP. There were not any congenital malformations in babies born to WNOEP. Among 11 children born to WNOEP 7 have been breastfed.
Conclusion: In our cohort, women with new-onset epilepsy may have an increased risk of perinatal hypoxia compared to pregnant controls. The risks were not increased compared to

women with epilepsy before pregnancy but was increased compared with healthy controls.

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Reproductive dysfunction in young men suffering from epilepsy

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Purpose: Epilepsy is a broad interdisciplinary problem. The pathology of the reproductive system in men with epilepsy can manifest itself both in the form of decreased libido, decreased fertility, erectile dysfunction, orgasm and ejaculation disorders, and lead to infertility. A decrease in free testosterone levels contributes to this dysfunction. The purpose of the study is to evaluate the effect of epilepsy and ASMs on male reproductive function.
Method: This study involved 30 men aged 18-44 years. All the patients selected for the study were divided into two groups. The study included neuropsychological testing using the Quality of life in epilepsy questionnaire-31 (QOLIE-31), a validated questionnaire "International Index of Erectile Function" (IIEF). The surrogate criterion for male fertility was a spermogram. EEG and EEG-video monitoring were used as screening methods.
Results: The average score on the IIEF questionnaire was 13.6 in group I, which corresponds to moderate erectile dysfunction. This measure was 22.8 in group II, which actually indicates a normal erection. The 11 (78.6%) patients from group I noted the absence of pronounced morning erections and weak masturbation erections, which allowed to exclude psychogenic erectile dysfunction. The men from the group II noted the preservation of morning erections. The erectile dysfunction is a common finding in young men suffering from epilepsy. Also, young men from group I were significantly more likely to have asthenozoospermia.
Conclusion: This study indicates the diversity of reproductive disorders associated with epilepsy. According to the results of the study, it was found out that erectile dysfunction and impaired fertility are more common in people with epilepsy since childhood and adolescence. This may be due to profound changes in neuroendocrine regulation under the influence of a long-term epileptogenic focus in the brain and prolonged exposure to ASMs.

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Peripartum seizures and multidisciplinary consideration of how to prevent them

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Purpose: Tonic-clonic seizures in labour are reported in 1-3.5% of women with epilepsy (WWE) and may lead to maternal hypoxia, fetal hypoxia and acidosis.

We describe our incidence of seizures in labour or up to 24-hours post-delivery and highlight key learning points.
Method: A database of all WWE who received pregnancy care (2017-2022) at St Thomas' Hospital was searched identifying those who had peripartum seizures. Demographics, medical history and pregnancy outcomes were documented. Each patient's case was reviewed with the multidisciplinary team (MDT) and learning points identified.
Results: Eight of 106 (7.5%) WWE had a peripartum seizure; 75% were primiparous. All described sleep deprivation as a historic trigger for their seizures. Two were taking lamotrigine; two levetiracetam; two a combination of both; two had stopped medications on confirmation of pregnancy due to fetal concerns. Median duration of seizure freedom prior to conception was four years, IQR 0.3-7.0. Four women had increased seizure frequency in pregnancy and their anti-epileptic drugs (AEDs) up-titrated. Five had low therapeutic levels; three had their doses up-titrated. Median duration of labour was 14 hours, IQR 5.0-15.3. Two sustained serious injuries (one head injury; one dislocated shoulder).

Key learning points identified by the MDT were:

- Consider lower threshold for up-titration of AEDs in those with low therapeutic drug levels; particularly considering pharmacokinetics of lamotrigine and levetiracetam.
- Discuss delivery plans with obstetricians to avoid prolonged labours; particularly in those undergoing induction of labour.
- Two patients considered to be 'low risk' had seizures. Therefore, all WWE should be counselled to have consultant-led peripartum care.
- Pre-pregnancy counselling allows women to make individualised informed decisions regarding pregnancy and risks/benefits of AEDs

Conclusion: We describe higher than published rates of peripartum seizures in WWE in women treated with lamotrigine and levetiracetam and propose learning points to be considered by the MDT and during pre-pregnancy counselling.

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Seizure control and pregnancy outcomes in women with temporal lobe epilepsy

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Purpose: To investigate the seizure control and pregnancy-related outcomes of Chinese women with temporal lobe epilepsy (TLE） and analyze therapeutic factors associated with increased seizures.
Method: We screened women with temporal lobe epilepsy enrolled in a retrospective registry of epilepsy and pregnancy (2009-2018) in West China hospital. Information including basic demographics, treatment, seizure control, pregnancy-related outcome, and 1-year follow-up

after delivery were documented in detail. They were classified into temporal lobe epilepsy with hippocampal sclerosis (group 1) and without hippocampal sclerosis (group 2). All data were analyzed by SPSS 26.

Results: 50 women contributing to 58 pregnancies were finally included. 36 pregnancies were in group 1, among which 13 underwent epilepsy surgery previously. No statistical differences were found in clinical profiles, seizure worsening, and pregnancy outcomes between these two groups. Of all subjects, seizure free was achieved in only 22.4% (13/58), while convulsive seizures increased in 38.6%（22/58）pregnancies and non-convulsive seizures increased in 31%(18/58) . Multivariate regression analysis showed that patients withdrawing anti-seizure medications (ASMs) during the first trimester could predict the increased frequency of convulsive seizure (odd ratios [OR] 7.16, confidence interval [CI]1.28-40.02, p=0.03). Surgery before pregnancy was more likely to have stable seizure control of either seizure (OR 0.16, CI 0.03-0.91, p=0.04) and most (69.2%,9/13) had uneventful pregnancies. Hippocampal sclerosis (OR 1.60, CI 0.47-5.51, p=0.46) and proactively adjusting the doses of drugs with high clearance rate (OR 0.53, CI 0.10-2.98, p=0.47) were not associated with seizure worsening. Although 3 had spontaneous abortions, no major malformation was found in these live children after 1-year follow-up.

Conclusion: Seizures were not well controlled during pregnancy in studied women with TLE due to poor management. It could be manageable by drug adherence and surgery before conception. Most patients who had eventful pregnancies still gave birth to healthy children.

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Progesterone and its derivatives for the treatment of catamenial epilepsy: a systematic review

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Purpose: Catamenial epilepsy (CE) is defined as an increase in seizure frequency during or just prior to menses. The treatment usually includes a combination of non-hormonal and

hormonal therapies. This systematic review summarizes the available data on the efficacy of progesterone and its derivates to treat CE.
Method: We performed a systematic search of the literature to identify studies reporting data on the use of progesterone and its derivatives (any type and dose) for the treatment of CE. The main outcome included the efficacy of progesterone and its derivatives on seizure frequency.
Results: Nineteen articles (457 patients) were included; four were randomized controlled trials (two comparing progesterone vs placebo and two comparing norethisterone vs placebo). Progesterone was generally administered during the luteal phase (from day 15 to 25) or during perimenstrual exacerbations (from day 23 to 25), with an average dose of 10-30 mg/day to a maximum of 300 mg/day. The therapy, usually well tolerated, was ineffective in the randomized controlled trials; conversely, it was associated with an overall reduction in seizure frequency in case reports and uncontrolled studies, whereas it.
Conclusion: Although sporadic evidence suggests that hormone therapy with progesterone may be useful in the treatment of CE, its efficacy has not been demonstrated in controlled trials. The possible antiseizure effect of progesterone could be mediated by its active metabolite allopregnanolone, making the plasmatic measurement of these hormones mandatory to evaluate efficacy. Further randomized controlled trials should investigate the efficacy of progesterone and its derivatives, addressing these pharmacological issues.

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Risk factors associated with uncontrolled seizures in Mexican women with epilepsy during pregnancy: case-control study

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Purpose: Epilepsy in pregnancy is a disease with maternal and fetal complications. The aim of this article is to describe the relevant modifiable risk factors in women with epilepsy during pregnancy in a Mexican population.
Method: Case-control study, conducted in Mexico. A total sample of 71 patients with 42 cases (epilepsy and seizures during pregnancy) and 29 controls (epilepsy without seizures during pregnancy). They were selected by inclusion, exclusion and elimination criteria. Normality tests were used for data distribution; intergroup comparison of variables was by T-test or Mann-Whitney test and conditional logistic regression models were fitted.
Results: The type of seizure onset was focal impaired awareness in 38% of cases vs. 51% tonic-clonic in controls P=0.030. Three months before pregnancy 50% of cases had had a seizure vs. 10.3% of controls P=0.002. During pregnancy, 59% of the cases had more than 2 seizures, with a difference of 1 month between each one in 40%, the mean WOG was 20.9±10.5. Thirty-one percent of cases had poor adherence to treatment with use of polytherapy in 81%

(65% with levetiracetam) vs 18% of controls P=0.043 (carbamazepine in monotherapy 34% P =0.010) and a urinary tract infection was identified in 59% vs 20% of controls P=0.001. After pregnancy resolution 14% of the cases presented seizures in the puerperium vs 3% of the controls and 59% of the cases continued in uncontrolled condition presenting at least 1 seizure per month P=0.000.
Conclusion: Focal epilepsy, pregestational uncontrolled period, number of seizures during pregnancy, poor adherence, polytherapy and lack of infection control are modifiable risk factors that influence the development of seizures during pregnancy in Mexican patients.

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Evaluation of the effectiveness of topiramate in the treatment of epilepsy in women of reproductive age

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Purpose: To evaluate the effectiveness of topiramate in the treatment of epilepsy in women of reproductive age.
Method: 78 women were examined, aged 18 to 52 years. The mean age of the patients was 28.6±11.4 years. To optimize therapy, taking into account the minimal effect of topiramate on the development of oncological diseases of the female reproductive system, we made a gradual replacement of the anticonvulsant drug valproic acid to topiramate at the rate of 3-5 mg/kg of body weight per day. At the same time, the average daily the dose did not exceed 200 mg/day.
Results: After 6 months of regular intake of topiramates at a dosage of 200 mg/day in group 1 patients, a decrease in the frequency of attacks from 8-10 to 5 attacks per month was noted. The dynamics of attacks was the best at 3-6 months of taking topiramate, and reached 1 attack per month by 6 months. In addition, patients noted a decrease in the duration of seizures up to 1 minute, with initial values up to 3-5 minutes. In group 2, we also noted a decrease in the frequency of seizures up to 3-4 times a month, however, the dynamics was lower than in group 1
group. Whereas in group 2, against the background of the drug valproic acid, an increase in the content of progesterone was not observed.
Conclusion: Against the background of topiramate in the group of patients with resistant the course of epilepsy, the values of estradiol were initially higher than those of progesterone. At the same time, in group 2, our studies showed the absence of a positive effect of valproic acid on the change in the progesterone / estradiol ratio, which maintained an insufficient level of clinical compensation for seizures in group 2 patients.

Epilepsy in Older People

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Idiopathic generalized epilepsies in elderly: young features on old background

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Purpose: Idiopathic generalized epilepsies (IGEs) are most commonly seen in children, adolescents and young adults, with well-defined criteria and management. Much less is known about its occurrence in the elderly, and generalized epilepsy has traditionally been thought to rarely develop as a new-onset seizure disorder in this age group. In this study, we purpose to identify common features of IGEs in elderly patients.
Method: This is a retrospective study on 370 elderly patients (mean age 70,25 ± 5,73 years) with epilepsy referred by a neurologist to our epilepsy center and followed between 2018 – 2022 at the National Epilepsy Center, Republic of Moldova. The patients were examined with a detailed medical history, neurological examination, EEG and neuroimaging.
Results: In our population, IGEs in the elderly people account about 4.05% (15 elderly patients). Patients were diagnosed with IGEs based on clinical semiology of seizures (myoclonic seizures, absence seizures and tonic – clonic seizure on awakening) in 3 patients (20%), and in the rest of them, exclusively diagnosed based on video EEG recording of seizures (myoclonic seizures) and interictal generalized discharged (bilateral synchronous spike and waves, or polyspikes and waves epileptiform discharges). The mean aged of seizures onset was at 16,66±8,05 years old, with an unusual case of seizures onset at 68 years old, and was common long term seizure freedom (21,5±7,93 years of remission). On neuroimaging all patients presented mild diffuse subcortical gliosis (Fazekas I), and 1 patient with parietal cavernoma.
Conclusion: In 80% of cases IGEs in elderly is diagnosed by EEG and they commonly are associated with frequent non-specific structural cerebral lesions and long-term seizure freedom during life time. Clinically, elderly with IGEs exhibit same seizure types like other age groups.

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Epilepsy in the elderly: clinical and therapeutic characteristics

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Purpose: The incidence of epilepsy in people older than 60 years is higher when compared with younger populations. They have unique clinical, etiologic and therapeutic characteristics. We aim to analyze elderly people with epilepsy since there are few research works in our country.
Method: We searched all electronic medical records from January 2015 to December 2022 of our clinic. We found 511 patients with epilepsy, 198 were older than 60 years at last visit and

we identify 93 patients with epilepsy onset after that age.
Results: Medium age of onset was 72 years old (60-89), more frequent in men (2:1).
All seizures were of focal onset, most of them were motor seizures with altered awareness (65%) and 21% had focal onset status epilepticus.
Epilepsy was lesional in most patients (63%), most frequent etiology was ischemic stroke (34%) followed by tumoral (9%). The etiology was unknown in 37% of patients.
EEGs were abnormal in 55 % of patients but only 27% had epileptiform discharges.
Most patients had cardiovascular risk factors (70%) and almost half had dementia (45%).
Most patients (84 %) were on monotherapy. Levetiracetam was the antiseizure medication mostly used (66%), followed by lacosamide (11%) and phenytoin (10%). Adverse effects were described in 26% of patients; the most frequent was behavioral changes and sedation in relation to levetiracetam.
Most patients (85%) had good outcome with treatment and were seizure free. Only 2 patients developed drug-resistant epilepsy.
Conclusion: We found history of ischemic stroke in 34% of patients with epilepsy onset in the elderly. We described good outcomes with monotherapy in this group age. These findings are similar to those previously published.

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Age-related epilepsy: characterization of a new model in rats

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Purpose: **Background:** With the increase in life expectancy, the prevalence of age-related pathologies, such as cardiovascular, cerebrovascular diseases and neuropsychiatric disorders are also on rise. Epilepsy is prevalent among elderly and associated with behavioral and cognitive impairments, reduced life quality, and an increased mortality rate. Nevertheless, age-related epilepsy is underdiagnosed and the underlying mechanisms are not clear. The blood-brain barrier (BBB) is a unique feature of the cerebrovasculature, regulating the passage of molecules between circulating system and the brain . We previously described a critical role for BBB dysfunction and TGF-bsignaling (BBBd) in epileptogenesis (Friedman, 2011, Epilepsia). Additionally, we showed in aged mice that BBBd is associated with slowing of neural network, lower seizure threshold and cognitive decline, while inhibition of TGF-b signaling reversed these neurological impairments (Senatorov et al., 2019, STM).
Purpose: Establish a new rat model for age-related epilepsy.
Method: In-vivo electrocorticography recordings were conducted in young (1-2month), middle-aged (8-12m), and aged (18-24m) WKY and SD rats. In a subgroup of aged rats electrocorticography was combined with intra-hippocampal recording. In-vivo T1-weighted (T1w) dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and ex-vivo T2-weighted

(T2w) were performed to assess BBB permeability and brain edema, respectively. Finally, a set of behavioral and cognitive tests were performed to test age-related social habits, anhedonia, and spatial learning and memory functions.
Results: Aged rats, but not young and middle-aged, presented spontaneous seizures in cortex and hippocampus, and paroxysmal slow wave events (PSWE). MRI showed age- and strain-dependent hyperintense T1and T2w signals, suggesting for age-related BBB dysfunction and edema. Finally, age-related epilepsy was associated with impaired social behavior.
Conclusion: We present here a new model for age-related epilepsy. Upon further validation, this model may be used for characterization of the disease manifestation, studying the underlying mechanisms, and discovering new biomarkers and treatments.

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Etiological profile and prognosis of new onset seizures above 60 years of age - a prospective study

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Purpose: Incidence of epilepsy and seizures is higher in the elderly than in other age group. Only few studies have focused on new onset seizures in elderly especially from Indian subcontinent and majority of them were retrospective.
The aim of this study was to study the clinical profile of new onset seizures in elderly and to determine etiology and the prognosis at 6 months.
Method: All consecutive elderly patients (more than or equal to 60 years) with new onset seizures who were either admitted in the hospital or seen in epilepsy clinic over 1 year (Dec 2017-Dec 2018) were included in the study. Seizure mimics, non-epileptic seizures and patients with past history of seizures were excluded from the study. We used the ILAE 2017 to classify seizures and found it is a convenient way of classifying seizures .
Results: A total of 50 consecutive patients were included in the study. When etiology was divided into broad categories, majority of the patients were grouped in Vascular etiology (n=20, 40%) followed by Unknown (n=18, 36%).8% each in subgroup of Metabolic and Infectious followed by Space occupying lesion (6%).Least common cause was Immune mediated (2%). Recurrence of seizures was seen in (14%) over a follow up period of 6 months.
Conclusion: Cerebrovascular events was the most common cause of seizures in elderly in our study. Majority of the patients were seizure free at 6months follow up indicating good prognosis.

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Pathways to care in epilepsy: a qualitative study in the Shai Osudoku and Ningo Prampram districts in Ghana

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Purpose: The study is part of a larger study, Epilepsy Pathway Innovation in Africa (EPInA) which is being conducted in Shai-Osudoku and Ningo-Prampram Districts of Greater Accra region, Ghana. The main objective is to explore the pathway to care in epilepsy and to describe the lived experiences of people living with epilepsy (PLWE) and their caregivers.
Method: A qualitative research design was employed for the study. Interview guides were developed for the various categories of respondents. The interview questions were constructed in English and conducted in English, Twi, Ga and Dangme. Oral histories were conducted with ten PLWE, four focus group discussions (FGD) were conducted with community members (male and female groups) and in-depth interviews (IDIs) were conducted with two healthcare practitioners, four caregivers, two traditional healers and two faith-based organizations (spiritualists). Participants were selected using critical case sampling and snow ball sampling techniques.
Results: It was revealed that many PLWE, caregivers and community members perceived epilepsy in diverse ways. In general epilepsy is attributed to a curse, diseases of witches, idols or gods. Due to the spirituality attached to epilepsy, the first place of care for PLWE is either a prayer camp or to see a traditional healer for prayers and herbal treatment respectively. However, the healthcare practitioners perceived epilepsy as a medical condition. Also, it was found that PLWE faced challenges, such as stigma and discrimination.
Conclusion: It is recommended that public education on epilepsy be intensified. Furthermore, there is the need to ensure that PLWE have access to improved healthcare in order to increase their quality of life.

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Does epilepsy contribute to the clinical phenotype of C9orf72 mutation in fronto-temporal dementia?

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Purpose: C9orf72 mutation is the most common genetic cause of Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS) worldwide. Recently, several reports of patients carrying the C9orf72 mutation, associated to FTD or motor neuron syndrome, who also manifested epilepsy, have been published. These observations raised the possibility that epileptic

manifestations are part of the clinical spectrum of the C9orf72 mutation, so we assessed epilepsy occurrence in FTD patients who carried the C9orf72 mutation and those who didn't.
Method: FTD was diagnosed according to the Rascovsky criteria for the behavioural variant FTD (bvFTD) and the Gorno-Tempini criteria for the variants included in primary progressive aphasia (PPA) form (semantic variant PPA (svPPA), logopenic PPA (lvPPA), nonfluent/agrammatic variant PPA (nfaPPA)).
Results: Eighty-four patients were diagnosed with FTD and checked for the C9orf72 mutation. PPA was diagnosed in 23 patients (5 lvPPA, 9 svPPA, and 8 nfaPPA) while bvFTD was diagnosed in 61 patients. The C9orf72 mutation was detected in 20/84 (23%) patients, including 20/61 bvFTDA patients and 0/23 PPA patients (p = 0.001).
Epilepsy was diagnosed in 6 patients (3 men and 3 women aged 64.5 + 6.1 years at the onset of FTD) and considered symptomatic according to ILAE Classification.
Prevalence rate of epileptic manifestations in all FTD patients was 7.1% (6/84). Epilepsy was more frequent in PPA patients than in bvFTD patients (4/23 vs. 2.61, p = 0.045) When we stratified the sample by C9orf mutation, epileptic manifestations were present in 2/20 (10%) patients who carried the C9orf72 mutation and in 4/65 patients (6.2%) who didn't (p = 0.6).
Conclusion: Our findings confirmed that epilepsy is part of the clinical spectrum of FTD but didn't support the possibility that epilepsy represents a characteristic feature of the C9orf72 mutation, as suggested by recent case reports published in the English literature. 10.1016/j.yebeh.2022.108783

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Elderly-onset epilepsy: clinical characterization of a special population

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Purpose: The incidence of epilepsy in elder people has steadily increased in the last few decades. Recently, it has been reported a bidirectional relationship between epilepsy and cognitive impairment and cerebrovascular disease. Our aim is to characterize clinically this population.
Method: Observational, descriptive study of patients with epilepsy onset ≥65 years, followed-up at the Epilepsy Unit of University Clinic of Navarre (Spain).
Results: We identified 43 out of 741 patients (5,8%). The main age at onset was 73,9±1.3 years (38% ≥75), with a median follow-up of 5.3±0.5 years. 95,2% had focal-onset epilepsy (temporal lobe 38%). Most seizures were focal with impaired awareness (52,4%) or focal to bilateral tonic-clonic seizures (42,9%). 14,3% suffered from epileptic status (4 focal non-motor, 2 focal motor). The most frequent etiology was structural 64.3% (vascular 50%). 28,6% had a past history of stroke, 26,2% cognitive impairment and 9,5% psychiatric comorbidity. Seven out of 10 patients who had a formal neuropsychological assessment showed any cognitive failure. Interictal EEG showed epileptiform activity in 45,3%. Brain MRI was

abnormal in 88% (38% small vessel disease) Thirty-four patients (74%) were on monotherapy and 60% achieved seizure freedom, Most used antiseizure medication were levetiracetam (35,7%) and lacosamide (33,3%) .
Conclusion: The most common identifiable cause of elderly-onset epilepsy was vascular. It was manifested with focal with impaired awareness to bilateral tonic-clonic seizures. A considerable number of patients associated cognitive decline. However, a great deal of patients remained without an etiological diagnosis. Most patients were controlled under monotherapy.

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Adams-Stoke syndrome as a cause of convulsive phenomena in an elderly patient, description of a clinical case in South America

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Purpose: Adams-Stokes syndrome effers to a sudden and transient loss of alertness, occasionally accompanied by seizures. It is named after two Irish physicians, Robert Adams (1791–1875) and William Stokes (1804–1877). We describe the case of a patient who comes for a syncopal episode of about 3 minutes accompanied by convulsive episodes for first time.
Method: Adams-Stokes syndrome effers to a sudden and transient loss of alertness, occasionally accompanied by seizures. It is named after two Irish physicians, Robert Adams (1791–1875) and William Stokes (1804–1877), The first description of the syndrome was published in 1717 by Marco Gerbec, a Slovene physician, who was cited 44 years later. by Giovanni Battista Morgagni.
Results: This is a female patient with heart failure and FEVI of 55% who presented a 3-minute syncopal episode with a subsequent convulsive episode and recovery of consciousness. A 12-lead electrocardiogram was performed showing complete av block.
Conclusion: The electroencephalogram did not show epileptic activity of any kind. We proceeded to take him to the arrhythmia room where they performed the implantation of a bicameral pacemaker without complications. The crises of this syndrome can be diagnosed by means of a meticulous clinical history, where paleness before the crisis and redness after them are reported. Crises are caused by lack of cardiac output due to: antimony poisoning, asystole, heart block, Lev's disease, or ventricular fibrillation. 7 The lack of blood flow to the brain is responsible for the loss of alertness. The definitive treatment is surgical, through the placement of a pacemaker. If undiagnosed or untreated, Stokes–Adams seizures have a 50% mortality within a year of the first episode. Convulsive phenomena do not require anti-seizure management once this is resolved by placing a pacemaker.

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Electroencephalographic changes in acute ischaemic stroke

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Purpose: To determine the association between changes in routine electroencephalogram (EEG) and ischaemic stroke localisation.
Method: 43 participants, 17(39.5%) women and 26(60.5%) men, treated for ischaemic stroke in the Hospital of Lithuanian University of Health Sciences Kaunas Clinics in 2022, were enrolled in this study. Mean age of study participants was 67.2±2.0 years. Routine EEGs were recorded up to 3 days after ischaemic stroke.
Results: Out of 43 EEGs 31(72.1%) had changes: 3(7.0%) had only non-specific diffuse changes, 27(62.8%) had non-specific focal changes and 1(2.3%) had specific focal changes. Anterior cerebral circulation stroke occurred in 32(74.4%), posterior circulation – 11(25.6%) participants. Hemispheric cortical lesions were identified in 18(41.9%) participants.
In case of anterior circulation stroke, EEG changes were identified in 24(75.0%) participants. In case of posterior circulation stroke, EEG changes were identified in 7(63.0%) participants (p>0.05).
Two(8.3%) participants with anterior circulation stroke had non-specific diffuse EEG changes, 21(87.5%) had non-specific focal changes and 1(4.2%) had specific focal changes. One(14.3%) participant with posterior circulation stroke had non-specific diffuse EEG changes and 6(85.7%) had non-specific focal changes (p>0.05).
Fifteen(83.3%) participants with hemispheric cortical lesions and 16(64.0%) participants without hemispheric cortical lesions had EEG changes (p>0.05).
Non-specific diffuse changes and non-specific focal changes in EEG were identified respectively for 1(6.7%) and 14(93.3%) participants with cortical involvement. 2(12.5%) participants with non-specific diffuse changes in EEG, 13(81.25%) – with non-specific focal changes and 1(6.25%) – with specific focal changes had no cortical lesion (p>0.05).
EEG patterns were the same in both, participants whose stoke localisation matched the location of focal EEG changes and those whose stroke localisation did not match the location of focal EEG changes (p>0.05).
Conclusion: There was no association between different patterns of EEG changes and characteristics of ischaemic lesions; however, further research with a larger group of participants and longer duration EEGs is needed.

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New onset seizures in elderly: a conundrum yet unresolved

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Purpose: With the advancing technology in this era, the average life span of Indians is currently 70.42 years, while Hong Kong leads the World by 85.29 years (2020). This parallels the rise in new onset seizures as well, which poses a challenge to diagnosis and treatment.
Method: The data were collected from the prospectively maintained records in the R.Madhavan Nayar Centre for Comprehensive Epilepsy Care, Kerala, South India over a period of 10 years from January 2010 to December 2020. The clinical, electrical and radiological data of individuals with new onset seizures above 60 years was collected and analyzed by dividing into 4 groups - Group A(60-79 years), Group B (70-79 years), Group C (80-89 years) and Group D (>90 years) using appropriate statistical methods.
Results: Of the total 311 patients, majority (49.8%) belonged to 60-70 age group and 65.9% were males. The most common seizure type was focal in 155 (55.5%) with majority (45.5%) presenting as focal motor with impaired awareness. Generalised seizure type was presented by 99 patients (35.4%) with 97.4% GTCS subtype. Seizure type was unclassified in 5 (1.7%) and 20 patients (7.1%) presented as status epilepticus. .Localisation related epilepsy was the major syndrome presented by 194 (65.3%) individuals (symptomatic 77.8%; Cryptogenic 22.1%). The most common etiology was post stroke seizure (34.7%), followed by unidentified (30.8%), Metabolic (13.5%), Vascular (7.3%), Space-occupying lesion/ metastasis (6.4%). Imaging was supportive in 57.5% and specific EEG abnormality was found in only 39.2%. Interestingly, 36 patients (11.5%) presented with atypical seizure semiology, 210 (80.4%) patients required only monotherapy and the overall mortality was 13.8%.
Conclusion: The elderly population has an enigmatic seizure presentation with limited corroborative information from electrical and radiological data, demanding special attention from the physicians.

Epilepsy in Resource-restricted Settings

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Improving detection and management of suspected epilepsy cases at primary healthcare in a rural African setting: a stepped wedge cluster randomised trial

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Purpose: The global treatment gap for epilepsy is largest in low- and middle-income settings (often >85%), partly contributed by stigma and lack of expertise in diagnosing and treating epilepsy. Capacity building of primary healthcare workers (PHW) may lower this gap and tackle stigma. These approaches have not been evaluated using a stepped-wedge cluster design in Africa.

Method: The WHO mental health Gap Action Programme Intervention Guidelines was used to train 172 PHW from 128 primary healthcare centres (PHC) in Kilifi County, Kenya on diagnosing and managing epilepsy and its psychiatric comorbidities. The 10-day training was conducted between June 2021- August 2022. Sixteen clusters, comprising 8 facilities each, were randomized to a 17-steps training period, followed by clinical supervision and 3-monthly refresher training. The primary outcome was cumulative incidence of new epilepsy cases diagnosed and managed at PHC with the total number of outpatient visits as the denominator. Secondary outcomes were changes in PHW levels of stigma, measured by changes in knowledge, attitudes and behaviour. Pre-trial baseline data were collected for two years. [Trial registration: Pan African Clinical Trials Registry [PACTR202011741472301].
Results: At baseline, the total number of new epilepsy cases was 359 vs 449 post-training. The cumulative incidence of new cases per 1000- population was higher post-intervention (1.41 95% CI= 1.28-1.54) vs (1.04, 95% CI=0.94-1.15), p<0.001. Post-training, PHW were more sympathetic towards people with epilepsy (PWE), β=0.40, 95%CI=0.18,0.62, p=0.00, more tolerant (β=0.63, 95%CI=0.40,0.86, p<0.01) and were less likely to view PWE as inferior or to endorse use of force or threats to handle them (β=0.65, 95%CI=0.47,0.82, p<0.01). PHW reported more positive intended behaviour towards PWE (β=0.69, 95%CI= 0.49,0.89, p<0.01). Detection of common neuropsychiatric conditions often comorbid with epilepsy also improved.
Conclusion: Capacity building of non-specialised PHW can lower the epilepsy treatment gap in resource-limited settings and address stigma among PHW. Funding: NIHR, grant# NIHR200134

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Use of a smartphone video application in the diagnosis of epilepsy and other neurological disorders: assessing clinical utility in high-resource and resource-restricted settings

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Purpose: This qualitative study evaluates accessibility, adaptability and utility of a smartphone-recorded video application in the diagnosis and classification of epilepsy and other neurological disorders in eight countries.
Method: A smartphone carer-recorded cloud-based video application, co-designed by neurologists and a technology partner, is utilised across 64 centres. 24,347 videos from 9,141 patients have been uploaded worldwide. Pilot studies, with local language capability, have

been implemented in United Kingdom, Germany, Ukraine, France, Pakistan, Australia, Canada, United States of America with St Lucia, and South Africa. Semi-structured interviews with international team leads explored local patient pathways, existing use of smartphone videos, barriers to technology implementation, and clinical utility of the application. Interviews were transcribed verbatim, reviewed and discussed by two research team members. NVivo 12 software supported qualitative analysis, identifying themes and subthemes within interviews.
Results: Interviews with international leads yielded 10 hours of recorded data. Common themes reported by all centres include reduced time to diagnosis, improved accessibility to healthcare and avoidance of unnecessary investigations, helping prioritise resource utilisation. Impact on clinician workload was consistently discussed, though opinions varied on whether this would increase or decrease. Challenges with clinical governance and importance of a secure video-transfer system were key themes amongst high-resource settings, while resource-restricted settings reported limited access to diagnostic investigations and translational challenges with application implementation. No centres considered smartphone access as a limitation to diagnostic technology, and all agreed access to a video storage system would be beneficial for clinician training.
Conclusion: Integrating a smartphone application aiding neurological diagnosis into any healthcare system will be met with challenges, requiring adaptations to overcome these and optimise clinical utility. High-resource and resource-restricted settings encounter unique barriers to application implementation, though experience similar benefits for patients and healthcare systems. Identifying setting-specific challenges and adaptations is relevant for implementing this technology into similar resource-restricted healthcare systems.

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Implementation of “recommendations for treatment strategies in people with epilepsy during times of shortage of antiseizure medications” in routine clinical practice in Kharkiv region

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Purpose: As a result of the war that russia unleashed against Ukraine on February 24, 2022, most of the Kharkov region was occupied, and Kharkov turned out to be a front-line city. This led to a shortage of medicines, including ASM. In May 2022, all centers that treat epilepsy resumed their work in Kharkiv. The situation with ASM was better than at the beginning of the war, but far from recovering, so the recommendations “Recommendations for treatment strategies in people with epilepsy during times of shortage of antiseizure medications” (Ali A. Asadi-Pooya et al. Epileptic Disorders 2022;5:751-64) were extremely helpful. The translation of the recommendations into Ukrainian and their publication on the website of the Ukrainian

League against Epilepsy contributed to simplifying the access of doctors to them
Method: Assess the possibility of implementing various sections of these recommendations in the Kharkiv region, which suffered significantly during this war.
Routine analisis
Results: The scheme of transition from oxcarbazepine to carbamazepine and from carbamazepine to oxcarbazepine is relevant, but well known in Ukraine. Eslicarbazepine acetate/oxcarbazepine/carbamazepine, clobazam/clonazepam, brivaracetam/levetiracetam, primidone/phenobarbital as ratios were interesting in cases of receiving humanitarian aid with drugs not registered in Ukraine. The section "Changing drugs to generics" was the most used. Rectal administration of ASM in emergency situations in dosage forms for other routes of administration was not used by us
Conclusion: Application of these recommendations is possible only in cases where it is impossible to follow commonly used clinical protocols, but in crisis conditions they were very useful. Of course, during periods of ASM shortage, the exchange of different ASMs can sometimes be considered as a risk mitigation procedure. Decision-making with regard to treatment and possible options should be driven by what is best for the patient.

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Collodion vs tensive-quality and cost comparison in 48 hour monitored ambulatory EEG studies

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Purpose: Compare the cost and quality of 48 hour ambulatory EEGs done with Tensive to those done using Collodion.
Method: This retrospective study included intermittently monitored 48-hour ambulatory EEG studies in 84 adults. The EEG studies were performed by EEG technologists with greater than 2 years of ambulatory EEG experience. In 50% of the studies, Collodion was used as the adhesive agent and Tensive was used in the other 50%. 23 disk electrodes were placed using the international 10-20 system and electrode impedances met the American Clinical Neurophysiology Society (ACNS) guideline of less than 10 kOhms at the start of the recording. The integrity of the electrode connection was assessed by evaluating the number of electrodes in which impedance exceeded 10 kOhms during the 48-hour study. The impedances were checked and documented every 4 hours, or more frequently if artifact was noticed by the R.EEG technologist during intermittent monitoring.
The cost per patient of using Collodion and its ancillary supplies was compared to the cost of using Tensive.
Results: The incidence of impedance greater than 10 kOhms was the same in the Collodion and Tensive groups during the first 24 hours. In the second 24 hours, the Tensive adhesive

had a higher incidence of impedances above 10kOhms: 35.7% compared to 28.6% for Collodion, but the difference is not statistically significant (p=.4834). The difference remains statistically insignificant for the entire 48 hours when controlling for EEG technologist (p=.4769) and patient gender (p=.5064). There is a 73% cost reduction per patient when using Tensive compared to Collodion.
Conclusion: There is no significant difference in electrode impedances between Collodion and Tensive during 48-hour ambulatory EEG studies.
Compared to Collodion, Tensive is more cost effective while maintaining the integrity of electrode placement and therefore, quality of the study.

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A clinical algorithm to separate focal and generalised epilepsy

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Purpose: Epilepsy type, whether focal or generalised, is important in deciding anti-seizure medication (ASM). In resource-limited settings, investigations are usually not available, so a clinical separation is required. We have used a Bayesian approach to devise an algorithm to do this.
Method: We used data on 29 clinical variables from 503 patients with defined epilepsy type as determined by an epileptologist with access to clinical, imaging, and EEG data. We calculated mutual information values and likelihood ratios for each variable, on part of the data, to devise the most accurate algorithm, and then calculated the accuracy of this on the remaining data.
Results: The best clinical algorithm contained 11 variables, and its accuracy was 92.2% in determining epilepsy type (sensitivity 92.0%, specificity 92.7%). Results of an algorithm incorporating just neuroimaging and EEG results achieved an accuracy of 83.7% (sensitivity 100%, specificity 34.1%).
Conclusion: This clinical algorithm is effective at separating focal from generalised epilepsy. It should be useful in resource-limited settings, by epilepsy-inexperienced doctors, to determine epilepsy type, and therefore optimal ASMs for individual patients, without the need for EEG or neuroimaging.

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Incidence of neurocysticercosis in a cohort of epileptic patients from South America

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Purpose: Neurocysticercosis is the disease caused by the infestation of the central nervous system by the parasite Taenia solium; This parasitosis is considered the main cause of acquired epilepsy in countries with a low Human Development Index. Objective: clinical characterization of neurocysticercosis in patients with epilepsy of a South American Hospital 2015-2018.
Method: All clinical records of patients with seizures who consulted the emergency department of a South American hospital to identify patients with epilepsy excluding those who did not have a simple cerebral CT report. The selected patients were determined sociodemographic, clinical and imaging variables through clinical records and telephone survey.
Results: 65 clinical records were identified that met the selection criteria. The median age was 38 years (RIC = 18-58), 75.2% were male, 90% of the patients were rural. The most frequent personal history was cardiovascular disease. The main etiology of epilepsy was cryptogenic (39.9%). The prevalence of neurocysticercosis was 20%. The most relevant finding in simple cerebral CT was the calcifications in 73.5%. No factors associated with the presence of neurocysticercosis were found in these patients.
Conclusion: The NCC is the third cause of epilepsy in this study and the second cause of acquired epilepsy, after cardiovascular. The factors associated with neurocysticercosis in this population could not be determined.

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Impact of epilepsy on quality of life of people with epilepsy in communities with high epilepsy prevalence in rural Cameroon

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Purpose: There is a dearth of data on impact of epilepsy on the quality of life of patients with epilepsy(PWE) in Cameroon. This study aimed to generate a comprehensive context-based data on the impact of epilepsy on the quality of life and to draw lessons for the mitigation of the impact.
Method: We conducted a community-based cross-sectional, descriptive and analytical study in 8 rural communities with high epilepsy prevalence in the Centre region of Cameroon. Quality of life was assessed using the quality of life in epilepsy questionnaires for adults (QOLIE-31-P version 2) and adolescents (QOLIE-AD-48 version 1). Multivariate logistic binomial regression was performed to identify factors influencing quality of life.
Results: Two hundred and one persons (201) were included in the study. The mean T-scores

for quality of life was 40.54±10.591. Most patients with epilepsy (79.1%) had a poor quality of life score. The most affected domains were seizure worry, cognitive function and social functioning. Higher seizure frequency, having a generalized seizure type, higher stigma scores and depression were all associated with poorer quality of life,
Conclusion: The impact of epilepsy on the quality of life of PWE in Cameroon is significant and multifactorial. Interventions to mitigate this impact must be multistrategic and not only focused on improving seizure control

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Exploration of dieticians' knowledge and perceptions regarding Ketogenic dietary therapy utilization in Kenya

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Purpose: Ketogenic dietary therapies (KDT) have been effectively utilized for children and adults with refractory epilepsy and are provided by an interdisciplinary team of healthcare professionals comprising a neurologist, a dietician, and a nurse. The role of the dietitian in the initiation and overall implementation is central to KDT therapy. These therapies hold the potential to bridge the large epilepsy treatment gap reported in Kenya but are rarely prescribed. This study aimed to establish the capabilities, knowledge, and experience of ketogenic dietary therapies (KDT) among dieticians in Kenya.
Method: This qualitative inquiry utilized in-depth interviews with purposively-selected consenting dieticians. A qualified team consisting of a social scientist, an interviewer, and a note-taker carried out the interviews. Inductive and deductive thematic analysis was conducted.
Results: This study enrolled 18 participants, the majority of whom (13) were aged below 35 years, had completed diploma-level training, and were engaged in clinical nutrition service. Fourteen participants understood the composition of KDT, eight of whom were clear regarding the utility of this intervention for the management of drug-resistant epilepsy in children. Cultural practices, poor public education on epilepsy, stigma, lack of dietician experience with KDT, and staffing shortages were perceived to be the main barriers to the widespread utili-

zation of KDT in Kenya. Formulation of locally adapted guidelines for KDT, patient education on KDT, and upskilling of dieticians to enhance their capabilities were considered the most impactful ways to improve the utilization of KDT. All participants were willing to participate in an online training program.
Conclusion: Dieticians in Kenya were aware of the KDT but the majority were not clear on its utility for the management of epilepsy. Barriers to implementation including lack of experience, cultural factors, and a poor practice environment were cited. To improve KDT uptake, government engagement, patient education, and upskilling of dieticians are required.

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Prescription pattern in a middle-income country: reasons for concern

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Purpose: The target of epilepsy treatment is to achieve seizure control with antiseizure medications (ASM). New ASMs lead to tailored treatment increasing tolerability and retention rate, though not efficacy. This study aimed to understand treatment options where novel ASM may not be available. For this purpose, we evaluated the prescription pattern of ASM in a pediatric population with drug-resistant epilepsy(DRE).
Method: We provide a descriptive analysis of data obtained at baseline (first appointment) from 198 consecutive infants, children, and adolescents (58.1 % male; mean age of 9.1 years [range from 2 to 18.9]) referred from secondary centers to treat DRE referred to a middle-income tertiary care center for a clinical trial.
Results: The mean seizure frequency was 143.49/month (IQR:4-920/ month), with a mean age at onset of 1.8 years. Most children (191 [96.46%]) were receiving polytherapy (2.94 ASM/child), with 138 (69.7%) receiving ≥3 ASMs. The most frequently prescribed ASM were valproate (51%), clobazam (41.9%), levetiracetam (35.4 %), lamotrigine (32.8%), carbamazepine (22.7%), and topiramate (22.2%). Second-generation ASM was the most common ASMs (176/198 [88.9%]). Forty-one (20.7%) children used first-generation ASM, and 31 (15.7%) with phenobarbital.
Conclusion: Although polytherapy is expected in DRE, combinations of three or more ASMs are a cause for concern, considering that second-generation medications are frequently used. The prescription trend in childhood usage with levetiracetam replacing sodium valproate was not documented. The use of older ASMs with more adverse effects and drug interactions may lead to a higher epilepsy burden.

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Frequency of different types of epilepsies presenting to tertiary hospital in Kashmir

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Purpose: About 70 million people are affected globally with epilepsy and about 1/6 of Indian population. Kashmir, being a resource poor state, extensive investigations(PET, SPECT, invasive EEG monitoring) cannot be done to rule out the cause of drug resistant epilepsy which comprises about 1/3 of those affected with epilepsy. By applying ILAE 2017 classification and by using minimal investigations in the form of EEG and MRI, management of 70% of the epilepsies can be done.
Method: Study was conducted in the department of Neurology in GMC Srinagar and data was collected over a period of 8 months fulfilling all the inclusion and exclusion criteria's for defining epilepsies. Demographic prolife , age of onset, family history, drug history and antecedent history(stroke, meningitis, encephalitis, trauma) was asked. MRI, EEG and metabolic workup was done.
Results: Among a total of 160 patients, 54.4% were males. Focal epilepsies were present in 57.50%, generalized epilepsies in 40.63%, unknown onset in 1.88%.
Focal motor were seen in 35.63%, non-motor in 21.88%, generalized motor epilepsies in 34.38%, generalized non motor in 6.25%.
In MRI brain, granulomas were seen in 10 %, post stroke sequalae in 10%,MTS in 7.5%, ICSOL in 4.4%, encephalomalecia in 2.5%, HIE in 2.5,FCD in 1.9%, autoimmune encephalitis in 1.9% , cortical atrophy in 1.9%, periventricular heterotopia in 1.3%, leukodystrophy in 1.3%, non-infectious granulomas in 0.6%, post infectious scaring in 0.6%. 53.75% had a normal MRI. Genetic testing WAS not done .Autoimmune profile was also sent
Conclusion: •By applying ILAE 2017 at the outset , a proper management of a majority of patients with epilepsy can be done.

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Making epilepsy a health priority in Kilifi county, Kenya by implementation of national guidelines on epilepsy management

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Purpose: Epilepsy has detrimental impact on people living in resource poor countries, yet up to 70% can achieve adequate seizure control with anti-seizure medications (ASM). The Intersectoral Global Action Plan (IGAP) is about making epilepsy a health priority through improving epilepsy care and reducing stigma. This study implements IGAP through dissemination and implementation of the Kenya National Guideline for the Management of Epilepsy to improve diagnosis, treatment and health outcomes of patients with epilepsy(PWE).

Method: With the support of the IBE Africa chapter and National Epilepsy Coordination Committee (NECC), we set out to implement the National Guidelines on the Management of Epilepsy in a rural poor setting, which has never been formally done. We signed a memorandum of understanding on adoption of the epilepsy guideline with the county government of Kilifi. The epilepsy guideline review team was formed and come up with diagnostics and treatment protocols for healthcare workers and informational materials for patients and caregivers. Epilepsy knowledge workshops were conducted in the study location.
Results: Two clinical management protocols for use by clinicians and an informational materials for patients and caregivers were developed from the guideline. i) ASM protocol for clinicians which provides information of indication, dosing, side effects of ASM, ii) Seizure identification protocol with suggested first, second and third line treatment, and iii) informational materials for caregivers and patients. Better compliance and improved participation in treatment process from caregivers was observed following workshops, and consistent use of the clinical management protocols.
Conclusion: The adoption of the epilepsy guideline by the department of health services Kilifi County is the first step to implement IGAP. This is hoped to reduce the treatment gap in this region and improve quality of life for PWE and caregivers. Through the NECC network, the protocols will be distributed in other counties in Kenya for adoption and implementation

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The feasibility of a philanthropic system as a global solution to help reduce the epilepsy treatment gap in developing countries

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Purpose: 35 million people worldwide currently live in the epilepsy treatment gap, recognised as a major public health concern by the World Health Organization (WHO). This is compounded by a global shortage of apposite neurophysiology specialists. Epilepsy requires clinical diagnosis, this can be expedited via supporting Electroencephalogram (EEG).
This study examined the practicalities and potential of building a highly efficient, entirely virtual, charitable organisation with a rapidly expanding global team of volunteer consultant clinical neurophysiologists, neurologists, paediatricians and technologists providing peer-to-peer advisory diagnostic services free of charge 24/7 to hospitals, clinics and patients-in-need in developing countries.
Method: Key metrics collated centrally include number of cases, use of system, time to respond, patient age, sex, status during examination and medication. Performance of projects, clinics, teams and volunteers tracked centrally, with case system reporting on all metrics automatically in real-time.
Results: The findings show TeleEEG® enabled 70 clinics in 25 countries over 10 years, leveraging £2 million worth of direct medical aid for epilepsy from £180,000 in benevolent donations. Reporting on 20,000+ cases, mean patient age 13 years old. Diagnoses were reported within an average of 2.5 days (2022) against a target of 5 days for routine cases, urgent cases

in 11 hours (2022) against a target of 24 hours. Mean time to respond, year-to-date January 2023, was 6 hours 33 minutes.
Conclusion: TeleEEG® is an innovative system of philanthropy, talent, technology and communication deriving medical aid from moments of time, garnered and synchronised across the globe in revolutionary provision. It achieves global resource levelling, matching need and available provision. TeleEEG® has proven its utility in the diagnosis of epilepsy in clinics in the developing world by developing a scalable, lean, global model powered by philanthropy and volunteerism for medical advancement in adversity, contributing to the reduction of the global epilepsy treatment gap.

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Ankylosis of temporomandibular joint in progressive encephalomyelitis with rigidity and myoclonus

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Purpose: This report describes ankylosis of temporomandibular joint in a patient with progressive encephalomyelitis with rigidity and myoclonus.
Method: Case report
Results: A 66-year-old man with a history of alcohol abuse presented with a progressive limitation of mouth opening, muscle rigidity and urinary retention for 16 days. He denied a history of animal bites and deep penetrating wounds. Both eating and speaking were difficult for him. And he developed repetitive and symmetrical myoclonus in the both lower limbs 3 days ago. Myoclonus mostly occurred spontaneously and the interval between attacks was about 10 seconds. In addition, myoclonic seizures could be induced by lower limb lifting or triggering by external finger tapping on the left below T10. Results of initial laboratory investigations, which included a full blood count, thyroid function, serum ammonia, blood vitamin status, autoimmune profile, syphilis and HIV testing, were negative. An analysis of the cerebrospinal fluid was normal, while serum and cerebrospinal fluid were positive for GlyR IgG antibodies (1:100). The open–closed lateral radiograph of the temporomandibular joint showed a significant limitation of movement of the condyle on the left side, indicating ankylosis of temporomandibular joint. Electroencephalogram and electromyogram were unremarkable, and no abnormality was found in brain and spinal magnetic resonance imaging. Anti-GlyR antibody-associated progressive encephalomyelitis with rigidity and myoclonus (PERM) was considered. Treatment with continuous intravenous administration of dexamethasone, oral clonazepam and baclofen were prescribed. Two weeks later, the patient's limited mouth opening was significantly relieved and he could walk independently without symptoms of myoclonus.
Conclusion: Progressive encephalomyelitis with rigidity and myoclonus may be a rare cause of ankylosis of temporomandibular joint which can be improved by immunotherapy and benzodiazepines.

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The initial treatment in convulsive status epilepticus in China: a multi-center observational study

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Purpose: To investigate the situation of initial treatment in convulsive status epilepticus (CSE) patients in China. And to discuss the difference of in-hospital outcomes and health economic costs between those with guideline-recommended initial treatment and those without.
Method: The retrospective study screened adult patients discharged with the diagnosis of status epilepticus (SE) from January 2016 to September 2022 in four centers in west China. Three neurologists collected the data from the medical record system by a structured case report form. Individuals with different exposure to initial drug were divided into benzodiazepine (BZD) and non-BZD group for outcome comparison. The primary outcomes were in-hospital mortality and the modified Rankin Scale (mRS) score at discharge. Secondary outcomes included in-hospital seizure control, refractory SE, in-hospital respiratory support rate, length of stay and cost of stay.
Results: Two-hundred and thirty patients with CSE were included according to the inclusion criteria. The mean age was 43.14 years and 138were male. There were 150 patients initially treated with BZD. Among the 27 used midazolam as initial treatment, 19 showed insufficient dosage. The other Eighty-eight patients used diazepam, of whom 12 were treated underdose. The other 115patients applied the antiseizure medications (ASMs) and/or coma-induced drugs as initial treatment. Among those initially administrated ASMs, intramuscular phenobarbital was applied in 33 patients, and valproate was adopted in 31 individuals. Significant difference in time interval from SE onset to first injection and etiology composition between BZD and non-BZD group.No significant difference in mortality or the mRS score was detected between two groups as well as secondary outcomes including health economic costs.
Conclusion: The non-adherence and underdose to the current SE guideline were very common in China. Intramuscular phenobarbital and intravenous valproate were still considered as the first choose in recourse-limited settings. The treatment practice was highly influenced by the etiology and treatment time interval.

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Semi-automated electric source imaging determines epileptogenicity of encephaloceles in temporal lobe epilepsy

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Purpose: Semi-automated electric source imaging (ESI) from long-term-monitoring (LTM) often achieves high detection rates of interictal epileptiform discharges (IEDs). Thus, averaged IED types attain high signal-to-noise ratios and allow propagation analysis early during the course of IEDs. We assessed whether ESI with propagation analysis is able to determine the epileptogenicity of temporo-polar encephaloceles.
Method: We retrospectively included 32 patients with temporal lobe epilepsy, who underwent presurgical diagnostics at the Epilepsy Centre Freiburg between 2010-2022. Temporo-polar encephaloceles were the only potentially epileptogenic lesions in 3 T MRI. Either intracranial stereo-EEG or Engel 1 outcome after resection of the encephalocele confirmed the definite epileptogenicity of the encephaloceles in 14/32 patients. LTM (duration: 6 ±2 days) was acquired with scalp EEG according to the 10/20-system with additional T1/T2 and in 23/32 patients with sphenoidal electrodes. IEDs were detected semi-automatically and clustered into IED types. The two most frequent IED types per patient (206 ±137 IEDs/type) were analysed. We performed ESI of IED types using a realistic three-compartment boundary element head model and two inverse methods (sLORETA, MUSIC). We counted a Euclidian distance ≥5 mm of ESI maxima with good signal quality (SNR >2, explained signal >60%) between IED type onset or half-rising flank and peak as propagation.
Results: ESI maxima, typically at the onset of at least one IED type per patient, correctly co-localized with an encephalocele in 18/32 patients (56%). During the course of IEDs, ESI maxima propagated from the temporal pole to other sublobar or extratemporal regions in 14/32 patients (44%), which suggests propagation starting within the encephalocele. ESI findings of the two different inverse methods validated each other. Sphenoidal electrodes showed highest signal amplitudes in 17/23 patients (74%).
Conclusion: Semi-automated ESI from LTM with 10/20 electrode coverage, especially with additional sphenoidal electrodes, is capable to determine non-invasively the epileptogenicity of temporal encephaloceles.

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White matter tracts quantitative abnormalities. Their relationship with postsurgical clinic outcome in patients with drug resistant focal epilepsies

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Purpose: To evaluate the relation between cerebral white matter tracts quantitative abnormalities and postsurgical clinic outcome, in patients with drug resistant focal epilepsies who underwent surgery to control the disease.
Method: Cerebral white matter tracts global and segmental characteristics were studied, using automated fiber quantification methodology in images obtained by magnetic resonance imaging performed in 15 patients, 6 with frontal lobe epilepsy (FLE) and 9 with temporal lobe epilepsy (TLE) who underwent surgery to control the disease.
Results: TLE patients had consistent segmental diffusivity anomalies in the ipsilateral inferior fronto-occipital fasciculus (IFOF), thalamic radiation (TR), inferior longitudinal fasciculus (ILF), and uncinate fasciculus (Un), furthermore the contralateral TR, cingulum hippocampus (CH) and Un. FLE patients had consistent global abnormalities of all variables in forceps minor of corpus callosum (CFMe). FLE patients with seizure freedom one year after surgery, had number of fibers higher values in ipsilateral TR and contralateral ILF, compared to patients with postsurgical seizure recurrence. The condition of seizure freedom after surgery in patients with TLE, was related to less values of mean diffusivity of ipsilateral IFOF, compared to patients with seizure recurrence.
Conclusion: Drug resistant focal epilepsy patients have cerebral white matter tracts global and segmental quantitative anomalies, that suggest the cerebral neural network compromise in this disease. These modifications are related with postsurgical clinical outcome.

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Surgical outcome of pharmaco refractory epilepsy in adults: a single center experience from Sri Lanka

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Purpose: Surgery is very effective for drug-resistant epilepsy. The National Epilepsy Center

(NEC) in Sri Lanka which offers an epilepsy surgical program was established in 2017.
Method: We report post-operative seizure outcomes, surgical complications, and impact on quality of life among 15 adult patients (≥16 years) who underwent epilepsy surgery at NEC. We used Engel classification and Quality of Life in Epilepsy 31 (QOLIE-31) questionnaire to assess seizure outcome and quality of life (QOL) respectively.
Results: Six female and 9 male patients underwent surgery [mean age 27.7 years, (range 16-44 years)] from October 2017 to June 2022. The mean follow-up duration was 32 months (range 6-55 months). Ten patients underwent temporal lobe resections. At 6-months follow-up, 80% (8/10) had favorable seizure outcomes with Engel class I or II. At one year follow up 6/8 patients (75%) and at two year follow-up, 5/7 patients (71%) had a favorable outcome. Five patients had extra-temporal lobe surgeries, and one of them was defaulted. Seizure freedom was observed in 4/4 (100%) at 6 months, 3/3 at one-year, and 2/2 at two year follow-up. Four patients (28.6%) experienced minor post-operative surgical site infections. Two (14.2%) had persistent quadrantanopia.

Meaningful improvement in QOL (change in QOLIE-31 score ≥11.8) was observed irrespective of seizure outcome or type of surgery (P value <0.001). QOL did not improve in one.
Conclusion: Epilepsy surgery is effective for selected patients with drug-resistant epilepsy and is an option in developing countries. Seizure outcomes in our patients are comparable to those worldwide. Further a clinically important QOL improvement was observed in our series.

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The expediency of using the method of the register for data collection about epilepsy patients which were operated on due to pharmacoresistance

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Purpose: Every year, we observe a trend towards an increase in the number of epilepsy patients requiring surgical treatment due to drug resistance in Ukraine. However, there are no accurate data on the number of such patients, the course of the disease, their pre-surgery evaluation, and the course of the postoperative period and long-term results of surgery.
Method: From 2014 to 2020, information was collected and analyzed about patients with drug resistance epilepsy. There was a study of the number of patients, the cause of drug resistance, and the method of surgical treatment. However, no information was provided regarding the subsequent course of the disease, the general condition of the patients, the number of seizures, and the use of antiepileptic therapy. With the aim of analyzing the effectiveness

of operative treatment of pharmacoresistant epilepsy, evaluating the long-term results of such treatment, maintaining constant contact with patients, and as a result of creating treatment recommendations for such patients, our team decided to develop a register for such patients.
Results: First of all, a questionnaire was created, which contains detailed information about the onset of the disease, its course, treatment, and information about diagnosis. This questionnaire became the basis for the creation of an electronic register for such patients, which allows you to enter all information about patients in an electronic database in a convenient and fast mode Wordpress. In 2021, the collection and processing of information began, which continues until now.
Conclusion: Having analyzed the collected information at this stage, we can conclude that the created register is able to work, relevant and appropriate. After all, it will help to make a logical and step-by-step way for the patient to receive surgical treatment, and will also become the basis for creating treatment recommendations for patients with pharmacoresistant epilepsy.

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Postoperative seizure and memory outcome for temporal lobe epilepsy with different subtypes of hippocampal sclerosis: a systematic review and meta-analysis

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Purpose: This systematic review and meta-analysis compared postoperative seizure and memory outcome for temporal lobe epilepsy with different hippocampal sclerosis (HS) subtypes classified by ILAE Consensus Guidelines in 2013.
Method: The study was conducted following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and registered in PROSPERO (CRD42022378779). Pubmed, Embase, Web of Science, and Cochrane Library were searched from January 1, 2013, to December 31, 2022. The outcome was completely seizure-free and improved outcome (Engel 1 or ILAE class 1-2) at ≥1 year after surgery. Studies were included if they had explicitly reported seizure outcomes and memory function evaluation among different HS subtypes. A random-effects meta-analysis with DerSimonian and Laird method was performed to obtain pooled risk ratio (RR) with 95% confidence interval (CI). Heterogeneity was explored in subgroup analysis by follow-up, age, and seizure outcome classification. The memory impairment was narratively reviewed because of various evaluation tools.
Results: Fifteen cohort studies with 2485 patients were eligible for the meta-analysis of seizure outcome and 7 articles described detailed assessment of pre- and postoperative memory within 6 cohorts. The pooled RR from very low evidence by the GRADE approach showed no significant difference of seizure freedom in HS Type 2 vs Type 1 (RR 0.98, 95% CI 0.84 to 1.15), Type 3 vs Type 1 (RR 1.11, 95% CI 0.82 to 1.52), or no-HS vs HS (RR 0.80, 95% CI 0.62 to 1.03) group with moderate to substantial heterogeneity, consistent with the analysis of im-

proved outcome (P >0.05). The long-term seizure outcome (≥5 years after surgery) and overall memory performance remained controversial.
Conclusion: Similar postoperative seizure outcome and disputable memory impairment was found among different HS subtypes based on the 2013 ILAE classification system. Multiple factors including but not limited to pathological changes, may influence the postsurgical seizure and cognitive outcomes.

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Is postoperative EEG a prognostic factor for seizure control in patients undergoing functional hemispherectomy?

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Purpose: Functional hemispherectomy (FH) is an effective surgical approach for children and young people with damage to an entire hemisphere, associated with refractory epilepsy or sleep status epilepticus. This surgery should be done as early as possible, to avoid the spread of damage to the healthy hemisphere.
The purpose was to evaluate the postoperative EEG as a prognostic factor for seizure control in patients undergoing FH, as well as to analyze efficacy and safety of FH in refractory epilepsy.
Method: 40 consecutive cases operated in between 2008-2020 through FH, with complete pre-surgical study for refractory epilepsy and a minimum follow-up of 2 years.
Results: The ages at the time of surgery ranged from 5 to 192 months (mean: 73 months), with an average of 46 months of seizures onset. 38 patients were operated with the University of California (UCLA) technique. 92.5% of the cases were free of seizures, including 3 cases that persisted with seizures and underwent a second disconnection surgery. Five cases (12.5%) had complications: 3 hydrocephalus requiring shunt, 1 venous thrombosis and 1 partial flap necrosis. All patients were able to walk during follow-up, but more than half lost their grasp on one of their hands. Two years after surgery, the post operative EEG showed interictal anomalies in 55% of patients (45% ipsilateral and 10% contralateral. No patient had interictal generalized epileptic activity), all of them were seizure free.
Conclusion: FH is a highly successful technique in seizure control, with a low morbidity rate and no mortality. The post operative EEG was not a prognosis factor for seizure free patients.

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Hemispherotomy in a patient with status epilepticus during sleep associated with congenital hemiparesis and unilateral polymicrogyria

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Purpose: Polymicrogyria (PMG) is one of the most frequently occurring brain malformations. Epilepsy occurs in 80%–90% of these patients. In extended PMG, an electrical status epilepticus during slow sleep (ESESS) can occur during childhood complicating pre-existing focal epilepsy. In drug-resistant epilepsies associated with PMG, surgical treatment can be offered to the patient, and have good outcomes, although we know that most patients are never submitted to a surgical approach.
Method: A 10 years-old boy, right-handed and hemiparetic in the left side of his body since birth. Had first absence seizure at 6 months, and his first tonic-clonic seizure, while he was sleeping at two years old. When he got seven years old, he presented ESESS criteria in sleep EEG, 1 seizure per month, always during sleep and started learning difficulties at school. MRI showed right hemispheric PMG, and three years later was submitted to right hemispherectomy.
Results: A correlation between ESESS and structural malformation exists, and PMG is the most common etiology. Thanks to the knowledge that ESESS usually remits before a mean age of 13 years medical treatment is considered sufficient in cases of ESESS encephalopathy. However, when ESESS is associated with a cortical malformation there is a low remission trend compared to nonlesional ESESS. In front of that, seems reasonable that patients with ESESS and PMG should be investigated to be submitted to hemispherectomy. In a case series of eighteen patients submitted to hemispherectomy, sixteen were seizure free and also had improvement in neuropsychological testing or had it stable.
Conclusion: Hemispherectomy can be helpful in patients with drug-resistant ESESS and hemispheric PMG. The main benefit is to definitively stop the seizure, so it should be performed after the failure of at least two appropriate AEDs

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Pathological findings in chronic continuous hippocampal DBS (Hip-DBS) for treatment of refractory temporal lobe epilepsy (TLE)

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Purpose: DBS has been increasingly used in the treatment of refractory epilepsy .Only a small number of patients submitted to continuous Hip-DBS had subsequently been submitted to resective surgery and their pathological findings were not described.
Method: A 19 years-old woman with intractable TLE received unilateral continuous DBS of the mesial temporal structures between March 2016 and August 2021. Preoperative workup showed interictal and ictal left temporal lobe onset associated to left mesial temporal sclerosis. She declined resective surgery and was submitted to left continuous Hip-DBS. After five years, she was submitted to cortico-amygdalo-hippocampectomy with removal of the stimulating electrode and an en-bloc resection of the mesial structures. Hippocampal sections

at the levels of the head and body were fixed in 4% formalin and embedded in paraffin. Five micrometres thick sections were evaluated for neuron density, astroglial reaction, microglia/macrophages, and lymphocytes with hematoxylin-eosin staining and immunohistochemistry to detect GFAP, CD68, and CD3, respectively.
Results: Histopathological analysis showed severe neuron loss in the granule cell layer, CA4, CA3, and CA1, and moderate loss in CA2, compatible with mesial temporal sclerosis type 1. An increased microglia/macrophage population was shown by CD68 staining with a predominant phenotype of activated cells. Staining against CD8 revealed no significant lymphocytic infiltration. Chronic hippocampal stimulation did not cause significant additional histopathological changes.
Conclusion: Chronic continuous Hip-DBS did not induce any additional histopathological abnormalities in the hippocampus. Its effects in seizure control are likely related to modulation of the epileptic network itself. The absence of new structural abnormalities is in line with clinical findings suggesting that Hip-DBS is safe in the long-term and that no further cognitive deterioration, including in memory, could be noted in patients submitted to Hip-DBS. A literature search did not find any report on pathological findings after chronic continuous Hip-DBS.

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EEG lateralization in predicting seizure outcome following hemispherotomy: a 15-year single centre observational study

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Purpose: Hemispherotomy is a common surgery for medically refractory epilepsy due to hemispheric diseases. Over 20% of these patients continue to have seizures following the disconnection. We have looked at the impact of the disease's etiology and laterality on the pre-operative EEG recordings and outcomes.
Method: In this retrospective study, we looked at 31 consecutive patients who underwent hemispheric disconnection in our institution. Their demographic details and clinical outcome on follow-up were collected from the electronic medical records. The pre-operative MRI brain, blood investigations, and genetic studies were assessed for etiology. A blinded expert assessed pre-operative and post-operative EEG.
Results: Of the 31 patients, 28 had a mean follow-up of 33.8 months (6 - 72 months). The etiologies were: inflammatory: 4 (12.9 %), vascular: 8 (25.8 %), acquired structural: 7 (22.6 %), and genetic structural: 12 (38.7%).Pre-surgical EEG showed ipsilateral inter-ictal epileptiform discharges (IED)in 17/31; the rest had contralateral/generalized IEDs. Ictal EEG showed ipsilateral onset in only 15/30 subjects.3 people lost follow up.Ipsilateral interictal EEG abnormalities in 15 patients had a positive predictive value of 100% for Engel 1 outcome. Even with contralateral or generalized IEDs, 8 of the 13 patients had Engel 1 outcome.

Gliotic lesions (13/31) were significantly associated with contralateral/generalized IEDs. The seizure outcomes were not significantly different between gliotic and non-gliotic etiologies. Of the four who had bilateral lesions in their MRI, 3 had Engel 1 outcome.
Conclusion: IEDs restricted to the side of the lesion predicted 100% seizure freedom. Though most gliotic lesions had contralateral or generalized EEG abnormalities compared to other etiologies, they did not have significantly poorer outcomes than others. Presence of bilateral MRI lesions and pre-operative EEG abnormalities on both sides do not necessarily predict poor seizure outcomes following hemispherotomy. Thus, in carefully selected patients with hemispheric epilepsy, hemispherotomy offers high seizure freedom.

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An interim analysis of real-world data on the use of vagus nerve stimulation therapy for the treatment of drug-resistant epilepsy in England

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Purpose: We describe the healthcare resource utilisation (primary objective) and clinical outcomes (secondary objective) associated with different Vagus Nerve Stimulation (VNS) Therapy devices for the treatment of drug-resistant epilepsy (DRE).
Method: This interim analysis is based on an ongoing multicentre, non-interventional cohort study involving prospective and retrospective data collection within five English centres. Adults and children with DRE who had a Demipulse®/AspireHC®, AspireSR®, or SenTiva® (with scheduled dosing feature) VNS device implanted were enrolled.
Results: This analysis includes 50 individuals from four centres; 26/50 (52%) were female. At VNS implantation, the median age was 13.7 (interquartile range [IQR]: 7.3–34.8) years. Most people were diagnosed with structural (16/49; 33%) or genetic (14/49; 29%) epilepsy. The median disease duration at VNS implantation was 8.3 (IQR: 5.0–15.5) years. The median age at diagnosis was 5.5 (IQR: 1.0–16.0) years. The median number of epilepsy-related treatments received in the 12 months prior to VNS implantation was 9.0 (IQR: 7.0–10.0). Amongst the 20 people with ≥1 comorbidity, the most common associated disorders were behavioural disturbance (11/20; 55%), depression (4/20; 20%) and hypertension (3/20; 15%). Intellectual disability was recorded in 28/50 (56%) individuals.
The median (IQR) time to achieve 1.5 mA therapeutic output current was 57.5 (42.3–89.5) days with SenTiva® (n=18), 96.0 (49.0–157.5) days with Demipulse®/AspireHC® (n=4), and 127.0 (73.0–223.0) days with AspireSR® (n=25). During the study period, most titrations with all devices occurred in the clinic setting (Demipulse®/AspireHC®: 34/34 [100%]; AspireSR®: 177/178 [99%]; SenTiva®: 313/343 [91%]), whilst 30/343 (9%) titrations with SenTiva® occurred remotely.

Conclusion: This interim analysis reports real-world demographic and clinical characteristics from people with DRE who received VNS Therapy. A numerically shorter time to achieve 1.5 mA therapeutic output current and more frequent remote titrations were observed with SenTiva® than other devices.

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First mild malformation of cortical development with oligodendroglial hyperplasia and epilepsy (MOGHE) description in Latin-American: a case series

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Purpose: Mild malformation of cortical development with oligodendroglial hyperplasia and epilepsy (MOGHE) is an emerging, highly epileptogenic pathological entity in drug-resistant epilepsy (Raghavendra S et al. Epileptic Disord 2021; 23 (2):407-411). While defining its clinical features remains an ongoing process, research demonstrates that patients with MOGHE often have lesions primarily impacting the frontal lobe (Schurr J et al. Brain Pathology 2017; 27:26–35). Despite a scarcity of reported cases in literature, knowledge about this entity continues to expand and additional clinical aspects are evaluated for their correlation with MOGHE. The following study presents a case series of five patients who underwent epilepsy surgery with MOGHE as the neuropathological diagnosis in their resected tissue.
Method: Descriptive analysis of clinical characteristics, EEG patterns, seizure semiology, radiological findings, surgical outcomes, and neuropathology description were conducted in a cohort of 5 Mexican patients that were diagnosed with MOGHE through neuropathology results in resected epilepsy surgery tissue.
Results: Seizure semiology correlated with EEG findings in all patients. All patients underwent surgery with focalizing interictal and ictal EEG patterns. All surgical cases showed increased subcortical cellularity of oligodendrocytes (Olig2 positive) with no proliferative activity, and heterotopic neurons in the white matter, without any other lesion. At one year follow-up, surgical outcomes revealed Engel IA (n=4), and IB (n=1).
Conclusion: Variation in our findings allude to an extensive pathology and a complex epileptic network in MOGHE patients. Surgical outcomes demonstrate lasting benefits. Knowledge of specific clinical-pathological features support our understanding of MOGHE patients.

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Surgical treatment of epilepsy with bilateral MRI abnormalities

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Purpose: Epilepsy surgery is an effective but underutilized treatment for drug-resistant epilepsy. Clearer understanding of surgical candidacy is required. In this study, we assessed the surgical outcomes of patients with bilateral MRI abnormalities, which is often considered to be a poor prognostic factor.
Method: This study was conducted at Severance Children's Hospital. Patients with drug-resistant epilepsy and bilateral MRI abnormalities were included. All patients underwent epilepsy surgery between October 2003 and October 2021. The age of seizure onset was 18 years or younger. Engel's classification was used to assess seizure outcomes at 1, 2, and 5 years after surgery. Factors related to post-operative outcomes were also assessed.
Results: A total of 80 patients met the inclusion criteria for this study. The median age at surgery was 8.6 (interquartile range [IQR] 6.1-13.6); median interval to surgery was 5.7 (IQR 2.1–11.5) years. Engel Class I outcomes were achieved in 44% (35/80), 51% (37/72), 50% (22/46), 48% (14/29) of the patients at 1, 2, 5 and 10 years post-operatively, respectively. Patients with shorter time interval to surgery and Non-Developmental and Epileptic Encephalopathy such as focal epilepsy, showed good surgical outcomes.
Conclusion: Approximately half of the patients with bilateral brain MRI abnormalities achieved seizure freedom after epilepsy surgery. The existence of contralateral brain MRI abnormalities should not hinder resective epilepsy surgery.

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Towards better definition of a resection strategy in pediatric LEATs causing refractory epilepsy

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Purpose: Resection strategy in pediatric long-term epilepsy associated tumors (LEATS) consists of pure lesionectomy, ECoG guided tailored resection or even partial/complete lobectomy. To propose an evidence based appropriate surgical strategy, we retrospectively analysed our consecutive institutional series of surgically treated pediatric LEATs.
Method: Twenty-two children suffering from medically intractable seizures harbouring suspected LEATs were investigated at the pediatric epilepsy monitoring unit using clinical and

video EEG monitoring, extended MRI epilepsy protocol and FDG and Methionine (MET) PET examinations. In 17/22 patients ECoG was used for tailoring the amount of resection.
Results: All children (mean age 8 yrs, from 2-18) were consecutively resected during a 3 years period. Lesions were located in the temporal lobe in 15 patients and extra-temporally in 7 patients. In temporal LEATS, mainly antero-temporal resections or temporal lobectomies were performed (15 patients), whereas in extratemporal LEATS lesionectomies or tailored resections guided by ECoG were achieved (7 patients). Histological diagnosis was GG in 20 and DNET in 2 patients. Preoperative MRI contrast enhancement was present in 10 GG (45%) and FDG PET showed a hypo-metabolic area in 6 GG (27%). Intensiv Methionine (MET) PET uptake was found in 13 GG, weak MET enhancement in 6 GG and no tracer uptake in 1 GG. In temporal resections, ILAE Class 1 seizure outcome was achieved in 75%, which was improved to ILAE Class 1 in 94% by performing 6 repeat surgeries with antero-temporal lobectomies after unsuccessful lesionectomies. The extratemporal patients experienced ILAE Class 1 seizure outcome in 86% without additional surgeries (mean follow-up 28 month).
Conclusion: In childhood LEATs amino acid PET was found to have high diagnostic sensitivity for GGs. In surgical therapy, for extratemporal LEATs a pure lesionectomy or tailored resection may be an appropriate strategy, but temporally, even a lobectomy may be necessary to achieve seizure freedom and avoid recurrences.

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Small craniotomy in the surgery for mesial temporal lobe epilepsy

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Purpose: Selective amygdalohippocampectomy for medically refractory mesial temporal lobe epilepsy is a well-established surgical technique. In recent years there has been a demand for less invasive treatment, with reports of small craniotomy and keyhole surgery. At our institution, we have begun using a small craniotomy in consideration of postoperative recovery and cosmetic aspects. We report on a small craniotomy for medial temporal lobe epilepsy at our institution and discuss the postoperative recovery status.
Method: The subjects were three cases of focal resection for medial temporal lobe epilepsy (two cases of hippocampal sclerosis and one case of cavernous hemangioma). A 10 cm skin incision is made from the upper border of the zygomatic arch to the superior temporal line. After incising the superficial and deep fascia of the temporalis muscle, allows exposure of the squamous temporal bone. Navigation system was used to identify the sylvian fissure, T1 and T2, where two bur holes was placed and small craniotomy was performed. The cortical incision was placed in T2 or T1 to approach the tip of the temporal horn using repeatedly navigation system. Finally the hippocampus and parahippocampus, and amygdaloid can be

removed. Postoperative recovery was assessed using food intake reflecting temporal muscle pain and general condition.
Results: All three patients were female, and the mean age was 47.3 years. There were no intraoperative manipulation problems with the small craniotomy and no perioperative complications. The mean time of recovery of food intake was 3.7 days in the small craniotomy group and 5 days in the six patients in the normal frontotemporal craniotomy group before the small craniotomy, indicating early recovery in the small craniotomy group.
Conclusion: The minimum invasive surgery technique is thought to reduce postoperative pain and mouth-opening limitation, suggesting that small craniotomy focal resection for medial temporal lobe epilepsy may be preferable..

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Ictal functional connectivity abnormalities in focal impaired awareness seizures

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Purpose: Both focal aware seizures (FAS) and focal impaired awareness seizures (FIAS) drastically impact patients' lives. The loss of consciousness in FIAS can be particularly devastating and is hypothesized to arise from widespread network dysfunction. However, the network changes during FIAS that may contribute to loss of consciousness are not fully understood. Evaluation of widespread brain network functional connectivity in FAS vs. FIAS may provide insight into strategies to prevent loss of consciousness in FIAS.
Method: Stereotactic electroencephalography recordings of 34 patients were obtained. All FAS and FIAS were extracted and divided into 20 second sliding windows across the entire seizure. Relative bandpower and connectivity were computed on seizure epochs. Metrics were z-scored to a patient's 10-minute resting state. Variability of relative bandpower and connectivity was calculated as the standard deviation of the metric across all windows. Regions sampled were parcellated into the ipsilateral and contralateral mesial temporal, lateral temporal, and frontoparietal association cortex (FPAC).
Results: FIAS were associated with greater relative bandpower variability in the contralateral lateral temporal cortex and mesial temporal cortex (2-sample t-test, $p<0.001$). Directional functional connectivity from the contralateral mesial temporal cortex to the contralateral lateral temporal cortex and FPAC ($p<0.05$). This may indicate that FIAS have exhibit disturbed connection between regions in the contralateral hemisphere beyond seizure spread. Addi-

tionally, FIAS had significantly greater functional connectivity variability from all regions to the contralateral mesial temporal cortex ($p<0.05$), perhaps suggesting that FIAS are more dynamic in nature.
Conclusion: This preliminary work demonstrates that FIAS exhibit more widespread changes than FAS and that these changes can involve areas distant to seizure spread. Interestingly, both the static and dynamic functional connectivity imply that the contralateral mesial temporal cortex may be more disconnected in FIAS. Further study of networks in FIAS may lead to neuromodulatory strategies to prevent loss of consciousness in FIAS.

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Epilepsy surgery outcome in temporal lobe epilepsy patients over 50 years of age

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Purpose: Epilepsy surgery (ES) is a well-established treatment option for drug-resistant epilepsy (DRE) (Alonso-Vanegas MA et al. Epilepsia 2017;58(1):10-18.). In this study, we describe our series of patients over 50 years old submitted to ES and examine outcome.
Method: We retrospectively collected and analyzed information on the presurgical evaluation (clinical history, seizure semiology, neurophysiological, neuroimaging, neuropsychological and psychiatric evaluation), surgical details, histopathology diagnoses, seizure outcome and anti-seizure drug(ASD) usage for temporal lobe epilepsy adult patients over 50 years of age operated at the International Epilepsy Surgery Center Hospital HMG Coyoacán, Mexico from 2009 to 2015.
Results: In total, 54 over 50 year old patients (48% females, median age at surgery: 53 years) were identified as having undergone resective temporal lobe surgery. The majority of patients underwent temporal lobectomy (38 patients) followed by selective amygdalohippocampectomy (16 patients). Left and right sides were equally affected and operated on. Hippocampal sclerosis (72%) and low-grade neoplasms (18%) represented the most common etiologies. Patients had a median epilepsy duration of 27 years with a median preoperative seizure rate of 12 seizures/month (IQR= 7). At one year follow-up (FU) 89 % of patients were Engel I; 67% of patients were seizure free (Engel IA) at 8-year FU, and 64% of these were off ASD. The preoperative and postoperative mean number of ASD used were 2.98 and 0.68, respectively.
Conclusion: Epilepsy surgery in patients over 50 years old is an effective and safe therapeutic option for patients with DRE. Our study confirms favorable outcomes. Likelihood of total seizure control classified by Engel IA is very high with this therapeutic approach.

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MALDI imaging mass spectrometry as a new tool for molecular histology in epilep-

sy surgery

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Purpose: Antiseizure medications (ASM) are effective in about 70% of patients with epilepsy. In a subset of patients with focal seizures resistant to ASM, epilepsy surgery is a safe and effective treatment and post-surgical seizure outcome is largely influenced by histological diagnosis. However, for certain pathologies, the diagnosis based on microscopic hallmarks remains challenging and their incidence and clinical presentation show several discrepancies among centers. Thus, there is an urgent need to integrate the standard neuropathological workup with new and unconventional techniques. **M**atrix **a**ssisted **l**aser **d**esorption/**i**onization **i**maging **m**ass **s**pectrometry (MALDI IMS) is a powerful technique for label-free bio-analysis used to investigate, in a single tissue section, the spatial distribution of thousands of biomolecules which can be correlated with traditional histological evaluation.
Method: To optimize "standard operating protocol" for MALDI IMS analysis of peptides on formalin-fixed paraffin embedded tissue sections (FFPE), we present preliminary experiments using tissue sections from patients with a histological diagnosis of type II Focal Cortical Dysplasia (FCDII), a developmental cortical malformation frequent cause of drug-resistance epilepsy. Histology and immunohistochemistry were used for a meaningful interpretation of the MALDI imaging data.
Results: Unsupervised classification of the spectra, achieved by hierarchical clustering or by principal component analysis, is able to differentiate distinct histopathological features, such as gray matter and white matter boundaries, the core of the dysplastic lesion and the adjacent perilesional area, as validated on immunoreacted-adjacent sections. Moreover, we show a good correlation between peptide intensity map and immunohistochemistry of the correspondent protein. We also identify a list of peptides that discriminate the lesion core from the perilesional tissue.
Conclusion: An optimized "standard operating protocol" for MALDI IMS on FFPE was developed to enhance spatial resolution and reproducibility. This will allow us to expand its applicability for different epileptogenic lesions more challenging in routine diagnostic practice.

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Advantages of laser induced thermal therapy (LITT) in children suffering from refractory epilepsy using a 3T intraoperative MRI suite

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Purpose: Laser induced thermal therapy (LITT) has become a minimal invasive treatment option in children with medically intractable epilepsy. But the transport of anaesthetized children from the operating room to the radiological suite makes the procedure challenging. Thus, we analyzed our experiences using a newly built 2 room intraoperative MRI sterile operating theater for implantation and lesioning procedures.
Method: During a 22 months interval we performed 11 procedures in 10 children, mean age 7.1 years (from 2 to 14 years), suffering from medically intractable epilepsy (2 harboring focal cortical dysplasia (FCD) in non-surgically amenable locations and 8 children had genetically proofed tuberous sclerosis (TS) harboring multiple tubers.
Results: All children had preoperative epileptological work up including invasive monitoring with depths electrodes in 10 TSC children to find out the most active tubera. In 8 procedures, 2 fibers were frameless stereotactically placed within the head frame, in 3 procedures, one laser fiber was placed into epileptological active tubers or the FCDs. The combination of stereotactic frame and head coil allowed the time saving and smooth positioning of the children into the scanner next door via a sliding operating table and a transport trolly, sparing repositioning. No complications were noted. Engel outcome was Grade Ia for both FCDs and Grade I-IV in the TSC patients.
Conclusion: All LITT procedures were successfully carried out without taking the children out of the head frame or the sterile rooms within a time frame of 3.5 to 5.5 hours. The intraoperative MRI suite clearly proofed advantageous for minimal invasive procedures, which normally need long transport of anaesthetized children between the operating suite and the radiological MR room.

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Post-traumatic stress-disorder in epilepsy: meta-analysis of current evidences

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Purpose: Patients with epilepsy are more frequently affected by psychiatric comorbidities, including anxiety, depression and Post-Traumatic Stress Disorder (PTSD). PTSD has a prevalence of about 4% in general population. To date, there are limited data on PTSD prevalence in epilepsy, including mainly studies with cohorts of adult patients or with non-standardized psychiatric evaluation. In our study, we aimed to provide updated estimates of the prevalence of PTSD in epileptic patients

Method: This meta-analysis was conducted in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We made a research on the online databases Medline (PubMed) using the words "PTSD epilepsy". We included studies published in English up to March 2022, which evaluated prevalence of PTSD in people with epilepsy. All included studies were assessed for risk of bias. After identifying all relevant articles, we extracted the following information onto a predesigned data collection form: (1) study design; (2) characteristics of study population (mean age, mean age onset epilepsy, number of subjects, duration of epilepsy).
Results: Out to 271 records initially found, 11 articles met inclusion criteria.
In seven studies the sample consisted of adults, in three were children and in one they were adults and children. Participants' mean age, which ranged from 10.3 to 51 years. Mean age at epilepsy onset ranged from 16.9 to 21 years. Mean duration of epilepsy ranged from 4.2 to 21.4 years.
The overall pooled prevalence of PTSD was 23,1% (95% CI: 10% and 36%). There was a high amount of heterogeneity of prevalence of PTSD.
Conclusion: In our meta-analysis, we found that epileptic patients are more likely to experience PTSD than general population. More studies with healthy controls are needed to clarify the relation between epilepsy and psychiatric outcome in pediatric population.

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Radiofrequency-thermocoagulation in pediatric epilepsy surgery: a review and pooled analysis

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Purpose: To conduct a scope review on radiofrequency thermocoagulation (RF-TC) in pediatric epilepsy surgery. In addition, due to the low number of dedicated pediatric series, to conduct a pooled analysis of cases published in the literature.
Method: We conducted a literature search using PUBMED and EMBASE which produced 470 results. Single articles were reviewed by title and abstracts, further selection by full article review. Reviews, conference abstracts, adult-only case series and other non-suitable publications were excluded. We excluded studies on hypothalamic hamartomas and non-RF-TC procedures such as stereotactic radiosurgery and laser interstitial thermal ablation. Stereotactic RF-TC and SEEG-guided RF-TC procedures were included. Case series and case reports with individualized data were further reviewed and pediatric cases (patients 18 years old or younger at procedure) were extracted for pooled analysis. Patient demographics, electroclinical and neuroimaging data, procedure outcomes, responder rates and complications were collected. Our unpublished experience in pediatric SEEG-guided RF-TC was included in the pooled anal-

ysis.
Results: We identified 18 articles for the literature review, 15 of them were selected for pooled analysis (68 cases). Sixty patients underwent SEEG-guided RF-TC. Mean age was 11.7 years (SD ± 4.5). Seizure freedom was achieved in 47.2%. Overall responder rate was 70.6%. Complication rates were low, transient neurological deficits were reported in 25%. No deaths were associated with RF-TC. Mean number of contacts where RF-TC was applied was 16.3 (SD ± 11.9). Though seldomly reported, volume of ablation was 4.3 cm^3 (SD ± 2.9) and the most frequent location was the insula.
Conclusion: There are few pediatric studies evaluating RF-TC. Safety and efficacy in children seem to be similar to that reported in larger adult series, although more studies are needed. Most cases reviewed where extracted from heterogeneous adult and pediatric series. Patients with small, high-risk surgical targets are ideal candidates for this procedure.

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Estimating the seizure onset zone in stereoelectroencephalography based on interictal markers and stimulated seizures

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Purpose: We investigated the role of interictal stereo-electroencephalography (SEEG) findings and electrically stimulated seizures in estimating the spontaneous seizure onset zone (spSOZ).
Method: We included 63 consecutive patients that underwent SEEG between 01/2013 and 03/2020 at the Helsinki University Hospital and had spontaneous seizures during the recording. We scored spikes, gamma activity, and background abnormality on each channel visually during a 12-hour interictal epoch containing wake and sleep. We categorized stimulated seizures as typical or atypical/unclassifiable, based on semiology, and, for typical seizures, we estimated the stimulated SOZ (stimSOZ). To assess whether stimSOZ and interictal findings provided complimentary information in predicting spSOZ inclusion, we fitted three mixed effects logistic regression models and compared the resulting areas under the receiver operating curve.
Results: The combined regression model incorporating the stimSOZ and interictal findings scored during sleep outperformed the models based on either marker alone ($p<0.001$ for both comparisons) in estimating which channels were part of the spSOZ. Of the individual predictors, the odds ratios (OR) for spSOZ inclusion increased the most if the channel was part of the stimSOZ (OR 60; 95% CI 37–97; $p<0.001$) or had continuous (OR 25; CI 12–55;

p<0.001) or subcontinuous (OR 36; CI 21–64; p<0.001) interictal spikes. At individual level the model's accuracy to correctly predict spSOZ inclusion varied markedly between patients (median accuracy 85.7, range 54.4-100), and this was not explained by etiology.
Conclusion: Combining visually rated interictal SEEG markers and stimulated seizures improves prediction of which SEEG channels belong to the spSOZ. Expectedly, inclusion in the stimSOZ and continuous or subcontinuous spikes increased the odds of spSOZ inclusion the most. Future studies should investigate whether the model's poor performance in certain patients can be explained by suboptimal sampling of the true epileptogenic zone.

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Mapping out the psychosocial adjustment process following epilepsy surgery through synthesis of the qualitative literature

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Purpose: Surgery is a well-established treatment for drug-refractory epilepsy. While the primary aim is to ameliorate seizures, it also has the potential to significantly impact psychosocial functioning. Qualitative research has been invaluable in understanding the lived experience of patients and the complexity of their post-operative psychosocial outcomes, yet it remains an under-utilised form of study. Here, we sought to synthesise existing qualitative research examining the psychosocial outcomes of epilepsy surgery to identify gaps in our knowledge and inform clinical practice.
Method: A search was conducted for qualitative research examining post-operative psychosocial outcomes for children and adults. Of 38 qualitative studies focussed on epilepsy surgery, 21 specifically examined patient and/or family experience of the post-operative period. All text labelled as "Results" or "Findings", including verbatim quotes, summaries, and theoretical interpretations were included as data. A thematic synthesis approach was used to conduct (i) line-by-line coding of text, (ii) organisation of codes into descriptive sub-themes, and (iii) interpretation of sub-themes to create higher-order "main" themes.
Results: Identified studies were published between 1965 and 2021, with a total sample of N=441. The majority were adult studies (n=16, 76%). Half (n=11, 52%) examined temporal lobe resections, with the remainder examining temporal and extra-temporal resections (n=5), frontal resections only (n=1), or hemispherectomy and callosotomy (n=3). Four main themes emerged; (i) reflecting on life pre-surgery; (ii) making gains post-surgery; (iii) the post-surgical adjustment process; and (iv) the lingering impact of epilepsy. These themes were drawn together to map out the short- (2-5 years) and longer-term (>10 years) post-operative adjustment process.
Conclusion: Despite heterogeneity in the type of epilepsy and surgical approaches, common themes emerged in how patients and their families adjust to life post-surgery. These findings

can help guide pre- and post-operative psychosocial counselling, and inform the nature of rehabilitation and support for patients and their families.

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Is ictal VEEG useful in pediatric epilepsy surgery? a retrospective analysis

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Purpose: Epilepsy surgery is a highly efficacious therapy in a selected subset of patients. The absence of clear-cut lesions, partial removal of the epileptogenic zone, and histology are clearly related to seizure persistence. It is still not clear the usefulness of semeiology and ictal EEG in the pre-surgical workup of pediatric patients.
Method: We evaluated all pediatric patients who underwent focal non-hemispheric surgery from 2020 to 2019 with at least a 3-year follow-up and a Long Term Monitoring with seizure recorded. We stratified the patients into four groups depending on age at surgery (0-5 y, 6-10y, 11-15y, and >15y). Semiology and ictal EEG was divided into whether they showed localizing/lateralizing feature or was not contributive. Two independent expert neurophysiologists reviewed blindly the video-EEG. A logistic regression evaluated the correlation between these features and seizure outcome.
Results: Seventy-two patients meet the inclusion criteria. 37/72 showed clear lateralizing signs, and 48/72 showed at least one localizing sign. In 40/72 it was possible to delineate a hypothesis regarding the lobe of origin. Ictal EEG was focal in 55/72 patients. The distribution was similar across age groups except for the presence of aura. Only lateralizing signs were associated with post-surgical seizure and drug freedom (p:0,04).
Conclusion: Seizure semiology and not ictal EEG are correlated to post-surgical outcome.

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Focal 18F-FDG-PET hypometabolism is a predictor of favourable outcome following epilepsy surgery

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Purpose: The prognostic value of preoperative focal hypometabolism with ^{18}F-fluorodeoxyglucose positive emission tomography (^{18}F-FDG-PET) is inconsistent.
Method: Patients with drug-resistant focal epilepsy investigated with preoperative 18F-FDG-PET were identified from a hospital database (n=46). Patients were divided into a 'PET-positive' group comprised of patients with focal 18F-FDG-PET hypometabolism concordant with Epilepsy Surgery Review Meeting consensus on surgical target (n=33) and 'PET-negative' group comprised of patients with normal or non-localising preoperative 18F-FDG-PET (n=13). Documented Engel and International League Against Epilepsy (ILAE) outcome scores at 12 months post-surgery were used to compare favourable outcomes (Engel class I and ILAE class 1 or 2) between groups. Subgroup analysis of 18F-FDG-PET concordance with MRI and EEG was performed.
Results: All 46 patients investigated with preoperative 18F-FDG-PET were included and group demographics were comparable. The odds of a favourable outcome following surgery was higher in the PET-positive group compared to the PET-negative group (OR=6.6,95%CI=1.26–34.54,p<0.05). Subgroup analysis showed the odds of favourable outcome following epilepsy surgery was also higher when a positive PET study was concordant with both MRI and EEG results compared to positive PET studies that were discordant with MRI or EEG (OR=6.9,95%CI=1.29–37.23,p<0.05).
Conclusion: Focal 18F-FDG-PET hypometabolism is a predictor of favourable outcome following epilepsy surgery.

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Epilepsy surgery program in Latin America, 20 years of experience: challenge and progress

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Purpose: Review of the experience of the Epilepsy surgery program in Uruguay.
Method: To analyze from the program database, focusing on surgery number, age, complexity, and outcome, in the periods: 1999-2009, 2010-2018, 2019-2022.
Results: The first 10 years, started to develop and increase knowledge and experience, 29 patients were operated on, 24 adults/5 children.
The main diagnoses were: 17 Mesial Temporal Lobe Sclerosis (MTLE), and 7 tumors.
Surgery performed: 16 temporal lobectomies (TLS), 1 selective amigdalo-hypocampectomy (SAH), 9 Lesionectomy with/ without Ecog, and 2 hemispherectomies.
Outcome: Engel I and II 96%.

Second period, the principal difficulty was the low referral to the epilepsy program, and the absence of economic support. We operated 52 patients: 40 adults/ 12 children.
The main diagnoses were 25 MTLE, 10 Malformation of cortical Development (MDC), and 7 tumors.
Surgery performed: 12 TLS, 11 SAH, 14 lesionectomy with/without Ecog, 11 hemispherectomies. Prolonged monitoring with subdural grid was starting.
Outcome= Engel I and II 82%.
The last period, the government started providing financial support, which allows an increased access to the program.
28 patients underwent surgery: 23 adults/ 5 children.
The main diagnoses were 10 MTLE, 9 MDC, 5 tumors. The first patients with MRI-negative were included. Surgery performed: 5 TLS, 3 SAH, 9 Lesionectomy with Ecog, 2 hemispherectomies, 2 subdural grid/Deep electrodes monitoring.
Outcome: Engel I and II 90%.
Conclusion: Despite the low number of surgeries, there have been 20 years of continued growth and development, with an increase in the number of procedures, and the complexity of cases and techniques, with similar results compared to other centers.
In the last years, governmental financial support was an important determinant of this growth.
Future challenges are the increasing number of surgeries, introduction or other technics, such as Steroelectroencefalography, palliative and minimally invasive techniques, which will result in a broader spectrum treatment.

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Intracranial interictal very high-frequency oscillations in rest and sleep

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Purpose: The objective of our work was to testify a hypothesis of interictal very high-frequency oscillations (VHFOs, 500 - 2000 Hz) being more specific biomarkers for epileptogenic zone compared to interictal high-frequency oscillations (HFOs, 80 - 500 Hz), on a large cohort of patients. In addition to that, we hypothesized that in sleep electroencephalographic (EEG) recordings, the occurrence of VHFOs might be higher than in rest awake state.
Method: Using intracranial EEG electrodes, we recorded interictal EEG oscillations between 80 Hz - 2 kHz in 104 patients with drug-resistant epilepsy in wakeful resting state (30 minutes recording) and in 35 patients during sleep. 21 patients in the rest study and 12 patients in the

sleep study met inclusion criteria for further evaluation of EEG data. We used power envelopes calculations and power distribution matrices to perform visual analysis of presence of VHFOs and HFOs.
Results: In wakeful rest invasive EEG (iEEG) study, patients with good postoperative outcome had higher percentage of resected areas with VHFOs compared to HFOs (75,94 % of areas with ultra fast ripples (1-2 kHz) resected and 64,33 % with very fast ripples (500 Hz-1 kHz), whereas only 49,27 % with fast ripples (200-500 Hz) and 38,82 % with ripples (80-200 Hz)). Occurrence of VHFOs in sleep iEEG recordings was higher than in rest analysis, however, in sleep, percentage of resected contacts in patients with good and poor outcomes did not significantly differ in any type of oscillations.
Conclusion: Interictal rest wakeful VHFOs are more specific biomarkers for epileptogenic zone compared to HFOs, according to our results. Even though interictal sleep iEEG analysis seems to be a more sensitive method for capturing VHFOs, it is also a method less precise in determination of epileptogenic tissue than rest wakeful iEEG analysis.

Supported by project nr.LX22NPO5107(MEYS): Funded by European Union – Next Generation EU.

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Outcomes of epilepsy surgery from a tertiary epilepsy center

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Purpose: Epilepsy surgery is a safe and effective therapeutic option in selected patients with focal refractory epilepsy. The main goal is to obtain seizure freedom, to reduce morbidity associated with anti-seizure medication (ASM) and seizure related mortality. We aim to evaluate a group of patients with refractory epilepsy who underwent epilepsy surgery and determine predictors of response.
Method: Retrospective study of patients submitted to epilepsy surgery between 2011-2021, in a Refractory Epilepsy Center. We excluded patients submitted to palliative surgery and neuromodulation.
Results: Seventy-five patients were included, 57.3% men (n=43), median age of surgery 41.6±14.3 years-old and interval between onset of epilepsy and surgery 24.0±14.8 years, with median follow-up of 6.5 years (IQR 5.0-8.1). Mesial temporal sclerosis, CNS malformations and long-term associated epilepsy tumors were the most frequent etiologies (53%, 12%, 12% respectively). 96% of patients were submitted to ressective and 4% to disconnective surgery. Of note, the correlation between MRI and neuropathology results was only moderate (K Cohen=0.52, p<0.001). One year after surgery, 56% of patients had reduction in ASM and 77% were seizure-free, decreasing to 68% after 10 years follow-up. 71% of patients had Engel I classification on the last appointment.
Etiology (p=0.005), type of surgery (p=0.011), localization of temporal vs extratemporal

(p=0.028) and frequency of seizures before surgery (p=0.024) were important to surgery success. Multivariate analysis was performed and frequency of seizures before surgery emerged as an independent predictor (p=0.042).
Conclusion: In our Center, epilepsy surgery allowed seizure freedom in a significant proportion of patients. Our results are in line with previously published studies.

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Quantitative methods to guide epilepsy surgery after invasive EEG: a systematic review

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Purpose: Many studies reported quantitative EEG analysis methods for improving the precision of surgical targets in drug-resistant epilepsy patients. However, none has been implemented in clinical practice yet. These methods are standardly validated on a retrospective cohort, with variable validation parameters. Besides the cohort size, validation parameters are rarely discussed, although they determine the reproducibility and the clinical utility of a method. We reviewed the quality of evidence in reported methods and propose validation strategies.
Method: We searched Scopus for research or conference articles published between 2017 and 2022. Studies validated on invasive EEG in a patient cohort were included. Studies presenting post-surgical outcome prediction without identification of surgical targets were excluded. Extracted parameters included cohort size, surgical outcome, epilepsy types, follow-up and the ground truth reference.
Results: From 830 studies, 82 met the inclusion criteria. Complete data were available in only five studies, while more than half of the parameters were missing in 14 studies. Cohort size varied from two to 123 patients (median=15) and minimum follow-up from 3 months to 3 years (median=1 year). One third of the studies did not include non-seizure-free patients (35%); for those that did, the median ratio of seizure-free to non-seizure-free patients was 1. Surgical resection was the ground truth in only 30% of the studies.
Conclusion: The principal cohort parameters should be clearly stated, as they directly represent the reliability of the results. Clinically relevant methods must consider a consecutive cohort, with minimal selection criteria. It is important to include non-seizure-free patients and various epilepsy types to ensure the applicability of the method. As the recurrence rate drops after 3 years, long follow-up ensures result stability. Finally, reports have demonstrated that the ablation of the seizure onset zone is not predictive of a good outcome. Thus, we suggest using the surgical resection as ground truth.

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Electrocorticography for tailored-surgery in drug resistant epilepsy with temporal encephalocele

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Purpose: Temporal lobe encephaloceles are increasingly recognized as a potential cause of medically refractory epilepsy and surgical treatment has proven effective. We describe two patients with drug-resistant temporal lobe epilepsy with temporal encephalocele who underwent a tailored temporal lobectomy.
Method: Patients underwent serial intraoperative electrocorticography (ECoG) recordings with strip electrodes placed on the temporal pole cortex before resection, on the surgical neocortical margin of the resection and, lastly, on the mesial temporal structures. Bipolar and referential electrode montages were reviewed to identify epileptiform activity and guide surgical planning.
Results: Patient 1, a right-handed 38-year-old male, presented with temporal seizures. Video-EEG long-term monitoring (VLTM) showed spikes and one seizure arising from the left temporal channels. 3T brain-MRI showed an encephalocele of the left temporal pole. ECoG showed sporadic spikes on the neocortical temporal surface before surgical resection, no epileptic activity was recorded on the amygdala and hippocampus. Therefore, the mesial structures were spared. Pathology showed FCD Ia. Engel Ia after 14 months.
Patient 2, a left-handed male of 20 years old at the time of surgery, presented with temporal seizures. 3T brain-MRI revealed a left mesial temporal pole encephalocele. VLTM showed frequent left temporal slow activity and spikes and 3 seizures with left temporal lobe onset. ECoG revealed frequent irregular spiking on the neocortical temporal surface before surgical resection and persistent epileptic activity on the posterior resection margin, so surgical procedure was extended until the sylvian vein. No epileptic activity was seen on the hippocampus thus it was spared. Pathology showed gliosis. Engel Ia after 10 months.
Conclusion: Resection of the encephalocele and associated cortex is often sufficient to provide seizure control. However, it's difficult to determine the extent of adjacent temporal lobe that should be respected. These cases demonstrate the usefulness of ECoG for a tailored surgical resection according to the irritative zone.

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Electroclinical features and surgical outcome of epilepsy in children with focal cortical dysplasia IIa

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Purpose: Focal cortical dysplasia (FCD) type IIa is a malformation of cortical development associated with drug-resistant epilepsy. The objective was to delineate electroclinical features and surgical outcomes at 12 months follow-up in a pediatric cohort with FCD IIa.
Method: Descriptive and analytical observational study of a cohort of patients with FCD IIa, followed (2005 to 2021) in a tertiary pediatric center.
Results: Thirty-eight patients under 19 years old were included. Median age of epilepsy onset 0.58 years. Median duration of epilepsy before surgery 3.66 years.
100% of patients had focal seizures, 55.2% had two or more seizure types, and 21% of children had evolution to bilateral convulsive seizures.
Neuropsychological assessments revealed cognitive impairment in 52.6% of children. At 12 months follow-up, test results showed stability in 84.2% and worsening in 15.7% of patients.
Interictal EEG showed focal unilateral epileptiform abnormalities in 71.1%, bilateral epileptiform abnormalities in 26.3%, and was considered normal in 2.6%. Postoperative EEGs improved in 50% of cases and showed no change in 39.5%.
Magnetic resonance imaging (MRI) showed abnormalities in 81.6%. This group had a significantly higher percentage of patients in Engel IA class at 12 months (p 0.0018).
Prior to surgery, 92.1% of individuals were on polytherapy. At 12 months of post-surgical follow-up, only 23.7% were still on polytherapy and 10.5% were free from all antiseizure medication.
At 12 months follow-up, 61.1% of patients were classified as Engel IA, a result comparable to similar studies that included adults and children.
Conclusion: Epilepsy related to FCD IIa has an early onset, and focal seizures can be of variable clinical expression. The pre-surgical evaluation should be performed as early as possible when this etiology is suspected. Results regarding control of seizures are significantly promising. At 12 months from surgery, the majority of patients did not show further cognitive deterioration.

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Auras in mesial temporal lobe epilepsy: correlation with postsurgical outcome

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Purpose: To determine the differences between characteristics of auras in patients with pharmacoresistant mesial temporal epilepsy (MTLE) who were in full remission after the resective treatment and patients who had seizures after the surgery.

Method: We conducted a retrospective study of 93 patients (42 males and 51 female) with pharmacoresistant MTLE who undergone surgical treatment and were postoperatively followed up for at least one year. All patients were divided in two groups according to the postoperative outcome: i) patients with full remission (ILEA 1, 81 patients, 87.1%), and ii) patients without remission (ILEA 2-4, 12 patients, 12.9%). We compared characteristics of aura which were obtained during the presurgical evaluation in those two groups regarding the postoperative seizure outcome. Similar to some other publication (Ferrari-Marinho T, et al. Epilepsy Behav 2012; 24:120-125) all auras were classified as: i) typical mesiotemporal (49); ii) lateral temporal (1); iii) extratemporal (3); iv) nonspecific (11); and v) multiple auras (17). There were 12 patients without any aura.
Results: We found no differences between those two groups regarding the typical mesiotemporal auras (75,6% vs. 62.5%; p=0.356), lateral temporal (1.1% vs. 0; p=1.000), extratemporal auras (3.7% vs. 0%; p=1.000) or multiple auras (18.5% vs. 16.7%; p=0.862). The distribution of nonspecific aura was significantly less frequent among the patients with ILAE 1 (10.1% vs. 37.5%; p=0.011) but there was no difference among the patients without aura (12.3% vs. 16.6%; p=0.676), or any type of aura (p=0.686).
Conclusion: The significance of aura in the diagnosis of mesial temporal lobe epilepsy is unquestionable, but its characteristics in the majority of cases are not decisive for the outcome after the surgical treatment of MTLE if all other results of the presurgical evaluation are concordant.

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Rasmussen syndrome: a longitudinal clinical and electrographical study of 68 patients

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Purpose: To longitudinally describe the electroclinical features of a series of patients with Rasmussen syndrome (RS) including symptoms at onset, EEG pattern, imaging findings, treatment, and outcome.
Method: A retrospective study was conducted in 68 patients with RS followed at a tertiary-care hospital between 2001-2022.
Results: Thirty-seven patients were male and 31 female. Mean age at onset was 6.1 years (range, 1-8.5).Onset was associated with focal motor seizures in 51 (76%) and febrile status epilepticus in four (5.8%). Atypical presentations were observed in 13 manifesting with hemiparesis without seizures (5;7.3%), dyskinetic movements (4;5.8%), absence seizures (7;10%), and epileptic spasms (2;3%). Fifty-nine patients (86%) developed epilepsia partialis continua

1.2 years after onset.
In the early period, interictal EEG showed focal epileptiform abnormalities in one hemisphere in 41 (60%), focal delta activity over the affected hemisphere with contralateral normal background rhythms in eight (12%), multifocal abnormalities in seven, and was normal in 12 patients. The ictal EEG showed a multifocal origin confined to the affected hemisphere in all. The early MRI showed abnormal cortical and/or subcortical hyperintense signals in T2 and Flair in 38 and basal ganglia T2 hyperintensity and atrophy in five. Seven patients had a focal lesion mimicking focal cortical dysplasia. Bilateral cerebral hemisphere involvement was observed in three patients, progressive unilateral cerebral atrophy in 32. All patient received intravenous immunoglobulin and hemispheroctomy was performed in 43. After a mean 13-year follow-up (range, 2-20), good surgical outcomes (Engel class I) were observed in 39/43.
Conclusion: The presence of unilateral focal and multifocal seizures without response to treatment at onset with an initial unilateral focal or multifocal EEG pattern prior to the presentation of epilepsia partialis continua and/or hemiparesis may predict these syndrome in evolution. Cases with an atypical presentation at onset were the most severe and developed epilepsia partialis continua in the early period.

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A 10-year history of leg dysaesthesia and complex regional pain syndrome due to insular seizures

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Purpose: Our objective is to highlight the semiology of insular epilepsy, a rare and frequently misdiagnosed seizure type. Insular epilepsies commonly go unrecognised due to their similarities with other seizure types and the limitations of scalp-EEG in capturing this deep brain structure.
Method: Our case-study establishes a diagnosis of insular seizures in a patient with a 10-year history recurrent stereotyped episodes of left leg dysaesthesias and associated left ankle eversion.
Results: A 53-year-old right-handed lady presented to the emergency department with a sudden onset severe right occipital headache and mild left sided weakness. Serial CT imaging confirmed an expanding right temporo-parietal haemorrhage 24 hours after admission. She was diagnosed with a right insular cavernoma.

Recurrent episodes of left leg dysaesthesia associated with left ankle eversion occurring up to 6 times per day for the preceding 10 years had previously been attributed to complex regional pain syndrome. Events were stereotyped, episodic and painful, with persistence of symptoms despite regional nerve anaesthesia. In the context of a new-found large right insular lesion, there was renewed clinical suspicion of insular epilepsy.

Continuous video-EEG documented the patient's characteristic paroxysmal symptoms with confirmation of an electrographic seizure arising from the right mid-temporal region.

The patient proceeded to cavernoma excision via right frontal craniotomy, resulting in seizure freedom.
Conclusion: We describe a case of left leg dysaesthesia and ankle eversion initially diagnosed as complex regional pain syndrome, but subsequently proven to be insular seizures arising from a cavernoma in the right insula. This case highlights the importance of retaining an open mind, re-visiting previous diagnoses and crucially, understanding seizure semiology in diagnosing a seizure disorder.

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Temporal lobe epilepsy with scalp video-EEG topographically non-concordant: specific anatomo-electro-clinical phenotype in the approach strategy for temporal lobe epilepsy spectrum

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Purpose: Bitemporal epilepsy (biTLE), a potential cause of Temporal Lobe Epilepsy surgery failure, is rarely associated with unilateral hippocampus sclerosis and could suggest dual pathology by not lateralizing ictal scalp EEG. Intracranial EEG can be considered in the presurgical evaluation. However, the identification of an anatomo-electro-clinical phenotype to select patients benefiting from iEEG at presurgical assessment is still poorly defined. This study aims to investigate presurgical electroclinical features of TLE patients with topographically discordant scalp EEG that can potentially identify true biTLE.
Method: We retrospectively reviewed 14 presumed unilateral TLE (UTLE) patients with bilateral ictal scalp EEG findings investigated by intracranial bilateral longitudinal electrodes. Demographic and electro-clinical characteristics were evaluated.
Results: We identified 14 TLE subjects (7 males, 7 females; mean age at seizure onset 15.14 ± 9.35 years-old; mean epilepsy duration 20.64 ± 15.78 years) who had been submitted to intracranial EEG recording to clarify the non-unilateral finding in the scalp-EEG. In 3 of the patients, biTLE was appointed as the diagnosis after intracranial investigation. In 7 of the patients with unilateral epileptogenesis resective surgery was performed. In the remaining 4, 3 had a VNS implanted and 1 had only one iEEG seizure registration. In comparison with the UTLE patients, BTLE were significantly older at the time of epilepsy onset ($p = 0.042$) and had a longer time of epilepsy ($p = 0.041$).

Conclusion: Not lateralizing ictal scalp EEG should alert about the possibility of a true biTLE also in presence of unilateral findings at brain MRI. Although intracranial investigation is a relevant tool to be considered to localize the epileptic region with a good risk-benefit profile, scalp EEG evaluation in conjunction with specific anatomo-clinical and neuroimaging phenotype can play a role in surgery decision-making without invasive recordings in some patients. Further studies are required to better define the optimal management strategy.

Genetics

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Precision medicine in epilepsy management: GET application (gene, epilepsy, treatment)

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Purpose: The aim was to develop a prototype of an application that identifies the significance of discovered genes for further consideration in the treatment plan of patients with epilepsy (precision medicine).
Method: MEDLINE was systematically searched for related publications from the inception to 1 April, 2022. The following search strategy was implemented (title/abstract): “epilepsy” AND “precision” AND “medicine”. The following data were extracted: genes, phenotypes associated with those genes, and the recommended treatments. Two other databases were searched to cross-check the retrieved data and add to the data: https://www.genecards.org and https://medlineplus.gov/genetics. Also the original articles of the identified genes were retrieved. Genes with specific treatment strategies [i.e., any specific drug to be selected or to be avoided and also any other specific therapies (e.g., diets, supplements, etc.)] were selected.
Results: A database of 93 genes, which are associated with various epilepsy syndromes and for which specific treatment strategies have been suggested, was developed.
Conclusion: A web-based application (a search engine) was developed accordingly that is freely available at http://get.yektaparnian.ir/ “GET (Gene, Epilepsy, Treatment)”. When a patient comes to the clinic with a genetic diagnosis and a specific gene is identified, the physician enters the gene name into the search box and the App shows whether this genetic epilepsy needs a specific treatment. This endeavor would benefit from input by experts in the field and the website should be developed more comprehensively.

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Dravet syndrome: clinical manifestations in older adults and effects of contraindicated medications use

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Purpose: •Dravet Syndrome (DS) is a rare, early-onset, treatment-resistant epileptic encephalopathy starting in 1st year of life.
•Speech and gait problems are common in adolescence. Adults may have parkinsonism characterized by bradykinesia, rigidity, postural instability, antecollis, camptocormia
•We evaluated the adult patients with DS to determine their phenotype as well as any correlation between their outcome and the number of years on contraindicated medications (CIM).
Method: •Prospective, cross-sectional, multicenter
Inclusion Criteria
•Patients diagnosed with DS and 18 years and older who were never exposed to antipsychotics.
Data Collection
•Instrumental gait analysis (pose-based algorithm)
•Parkinsonian features through modified Unified Parkinson Disease Rating Scale (mUPDRS)

•Epilepsy characteristics (seizure frequency, types of seizures, number of episodes of SE)
•Functional mobility scale
•Adaptive behaviors (Vinelands-3)
•Screen for social communication deficits (SCQ Lifetime) and potential psychiatric/neurodegenerative disorders (Moss-PAS Checklist)
Statistical Analyses
•Logistical regression (Spearman r), multivariate analyses, Fischer tests, one-way ANOVA
Results: •60% of caregivers noted a loss of previously acquired skills as patients aged.
•Old age and use of CIM in the first 5 years of life were independently associated with worse adaptive skills and parkinsonian manifestations.
•77% of adults have social communication deficits
•Between 10-15% of adults with DS screened positive for dementia, depression and schizophrenia.
•VABS did not capture motor dysfunction that was observed with mUPDRS and gait analysis making it a weak substitute for evaluation of motor response in precision medicine trials.
Conclusion: Taken together, evaluation of adults suggests a progressive deterioration of adaptive behavior skills, parkinsonism, social communication deficits, and gait. In addition, use of CIM early in is associated with worse adaptive skills and parkinsonian manifestations highlighting importance of early diagnosis.

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Genetic testing and precision medicine for epilepsy in a private third-level hospital

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Purpose: To describe the use of genetic testing and precision medicine for epilepsy in a private third-level hospital.
Method: Descriptive, retrospective, observational, cross-sectional study. Inclusion criteria: patients with genetic epilepsy from January 2017 to January 2023. Data were obtained from clinical records. Tests (measures of central tendency, chi-square) were applied in SPSS software.
Results: 514 patients with epilepsy were included, 87 patients (16.9%) had genetic epilepsy. Age: mean 13.2±4.2, range 1-45 years old. Female: 50 (57.5%). Children: 67 (77%). Adults: 20 (23%). Family history of epilepsy: 9 (10.3%). Type: focal 21.8%, generalized 72.4%, combined 5.8%. Drug-resistant epilepsy: 10 (11.4%). Intellectual disability: 83%. Epileptic syndromes 55 (63.2%): developmental and epileptic encephalopathy (1.8%), benign familial neonatal seizures (1.8%), West (5.4%), Lennox Gastaut (5.4%), Febrile seizures plus (1.8%), Dravet

(3.6%), Doose (3.6%), Rolandic (3.6%), Janz (25.4%), Child absence (45.4%), Juvenil absence (1.8%). Genetic syndromes 16 (18.3%): Rett (6.25%), Usher type 3 (6.25%), Lafora (6.25%), Noonan (6.25%), corpus callosum dysgenesis (12.5%), Sturge Weber (12.5%), tuberous sclerosis (18.75%), Down (31.25%). Genetic testing 10 (11.4%): gene mutations in SCN1A, SCN2A, DNM1, PNPT1, TSC1, EPM2A and chromosomopathies at 4 (insertion), 15 and 21 (duplication), X (microarray). Better target anti-seizure medications (80%): avoid sodium channel blockers (SCN1A), cannabidiol (SCN1A), phenytoin (SCN2A, DNM1, PNPT1), vigabatrin (TSC1), valproate (EPM2A), everolimus (mTOR). Correlations were found: precision medicine and controlled seizures; precision medicine and better neurodevelopment ($p<0.05$).
Conclusion: More than half of epilepsies have genetic bases, including those classified as idiopathic, focal and lesional forms, as well as epileptic developmental encephalopathies. In our study, patients under precision medicine in genetic testing for epilepsy presented reduction of seizures and better neurodevelopment. Genetic tests are available for most developmental epileptic encephalopathies and it may influence positively in targeted treatment towards the precise molecular pathogenesis (precision medicine) (Orsini A, et.al. *J Transl Genet Genom.* 2018;2:16).

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A SCN2A loss-of-function variant causing early infantile onset encephalopathy

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Purpose: Mutations in the voltage-gated sodium channel $Na_v1.2$ cause a phenotypic spectrum encompassing epileptic encephalopathy and intellectual disability or autism without epilepsy. Early infantile onset encephalopathies are generally well respondent to sodium channel blockers, assuming a gain-of-function mutation. We evaluated an*SCN2A*: c.4976C>T (p.A1659V) pathogenic variant found in two infants non-respondent to carbamazepine.
Method: The mutation was identified through Next Generation Sequencing and inserted in the Pir cmv SCN2A plasmid encoding for $Na_v1.2$. HEK293 cells transfected with WT and mutated (A1659V) SCN2A were stained with anti-PanNaV antibody for immunofluorescence or lysated for Western blot assay. The immunofluorescences were acquired both at the epifluorescence and confocal microscopy. For functional characterization, $Na_v1.2$ WT and A1659V mutant were expressed in HEK293 cells and membrane currents were evaluated by whole-cell patch-clamp technique. Cells were stimulated with constant pulse-potentials ranging from -60 to +30 mV, D=10 mV, holding potential was -90 mV ($n\geq12$ experiments).
Results: SCN2A A1659V mutation does not impact channel expression. Whole-cell conductance (GNa) was calculated as GNa = I/(V – Erev), where I is the measured peak current, V is the step potential, and Erev is the calculated sodium reversal potential predicted by linear regression of the I-V curve for each cell. To calculate voltage dependence of activation, nor-

malized GNa was plotted against voltage and fitted with the Boltzmann function G/Gmax= (1 + exp[(V – V1/2)/k])−1 , where V1/2 indicates the voltage at half-maximal activation and k is a slope factor describing voltage sensitivity of the channel. Expression of A1659V induced a smaller current with respect to WT. Quantitative analysis of A1659V activation properties shows a shift of V1/2 about 10 mV towards more negative potentials and a time constant slower than the WT channel.
Conclusion: SCN2A loss-of-function mutations may cause a severe phenotype. Functional characterization may direct clinical interventions and expand funotype-phenotype correlations.

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Metabolic basis of pediatric developmental and epileptic encephalopathies (DEE)- genetic variant analysis in a South Indian cohort

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Purpose: Epilepsy is seen in patients with inborn errors of metabolism and metabolic dysfunction is crucial in brain disorders. These can present as developmental epileptic encephalopathy (DEE) or distinctive phenotypes- infantile spasms. The detection rates of metabolic causes of DEE using next generation sequencing has been rarely reported.
Method: A prospective hospital based study was carried out in 385 children with DEE, who underwent genetic testing (whole exome sequencing in trios- 71 and clinical exome sequencing- 314). Metabolic disorders were evaluated with biochemical assays and when required cerebrospinal fluid estimations were performed.
Results: A total number of 154 pathogenic/likely pathogenic (P/LP) variants in 385 children were identified; of which, 90 were diagnosed with suspected metabolic disorders. P/LP variants in metabolic genes were identified in 39 out of 90 (43.3%) and promising variants of uncertain significance in 29 (32.2%). Of these patients, onset of seizures less than 6 months of age was noted in 44.4%. These included variants for progressive myoclonus epilepsies (PME) (21; 53.8%) in *ACOX1, EPM2A, CLN1/PPT1, CLN2/TPP1, CLN3, CLN5, CLN6, CLN7/MFSD8, GBA, POLR3B, GLDC, KCTD7, L2HGDH*, *MT-TL1, NHLRC1, PLP1*; DEE unclassified with focal/multifocal seizures (9; 23.1%)- *SUOX, ITPA, AP3B2, SLC35A2,* Ch16p13.2 duplication syndrome, *ABCD1, NDUFV2*; generalized epilepsy (5;12.8%)- *SLC2A1, PTS*; early myoclonic encephalopathy (2; 5.1%)- *POLG, MFF;* LGS (1; 2.6%)- *ARG1;* West syndrome (1; 2.6%)- *BTD.* Biochemical tests were confirmatory in only 15.2% and 3 out of 17 who underwent skin biopsies for PME syndromes were confirmatory (17.6%).
Conclusion: Our cohort demonstrates for the first time from the Indian subcontinent that identification of metabolic variants can guide investigations and therapeutic implications in patients with variable DEE phenotypes. The highest yield is noted in phenotypes such as PME,

DEE unclassified and mitochondrial cytopathy. A high utility is noted given the low yield of available biochemical tests indicating cost-effectiveness of this approach.

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Expanding the clinical and phenotypic spectrum of *CHD2*-associated early onset epileptic developmental encephalopathy

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Purpose: The present study was performed to elucidate the phenotypic presentations and molecular genetic characteristics of *CHD2*-related epilepsy.
Method: A total of 13 paediatric epilepsy patients from 12 families were recruited from May 2015 to January 2023. Monoallelic variants in the *CHD2* gene were identified by whole exome sequencing (WES) and validated by sanger sequencing.
Results: Here, we present the molecular and clinical characteristics of 13 additional individuals from 12 families with de-novo pathogenic or likely pathogenic variants in the *CHD2*. A total of 10 mutation sites were identified among 13 cases, of which eight mutation sites were previously unreported. All individuals are presented with intractable early infantile-onset seizures, severe global developmental delay, and intellectual disability. Psychiatric disorders affected more than half of patients including autism spectrum disorder (ASD; 7/13, 54%), and attention deficit hyperactivity disorder (ADHD; 7/13, 54%). Photosensitivity was also observed in some patients (7/13, 53%). Other variable features include status epilepticus (3/13, 23%), motor impairments (8/13, 62%) such as hypotonia (4/13, 31%) and hypertonia (3/13, 23%), coarse facial features (3/13, 23%), constipation (4/13, 31%), and kyphoscoliosis (3/13, 23%). Four individuals (31%) had difficulties with walking, sitting, and fine motor skills. We report the first *CHD2* mutations in Cypriot, Turkish, Georgian, and Azerbaijanian populations. We suggest a novel variant c.2612G>A as a new potential hotspot mutation of *CHD2*, which

was found across different ethnic populations.
Conclusion: Monoallelic variants in *CHD2* cause distinctive epileptic encephalopathies characterised by multiple seizure types, and neurodevelopmental disruptions with varying degrees of intellectual disability, global developmental delay, Autism Spectrum Disorder (ASD), and Attention Deficit Hyperactivity Disorder (ADHD). Clinical heterogeneity among participants suggests that there is insufficient evidence to consider *CHD2* only as the photosensitive epilepsy gene. The present study expands the existing *CHD2* genotypic and phenotypic spectrum.

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Functional and structural characterization of variants of uncertain significance identified from whole exome sequencing of developmental and epileptic encephalopathies in an Indian cohort: an *in silico* approach

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Purpose: Developmental and epileptic encephalopathy (DEE) refers to a group of rare, sporadic neurodevelopmental disorders with early infantile onset. Whole-exome sequencing (WES) is the preferred method for the molecular diagnosis of these disorders since they are characterized by significant clinical and genetic heterogeneity. The detection of a large number of variants of uncertain significance (VUS) from these next-generation sequencing techniques and their use in clinical contexts is still challenging. Here, we are proposing an *in silico* approach to reclassify the VUS identified from WES into promising VUS and incidental VUS.
Method: WES analysis was performed for 97 probands including 90 trios. The variants were classified according to ACMG classification criteria. The *in silico* functional and structural analysis of a novel *de novo* VUS identified in the *STXBP1* (c.A434C:p.Y145S) gene of a female proband diagnosed with genetic DEE with myoclonus ataxia was performed. The impact of VUS on protein stability, interactions, and structure was detected using iMutant, STRING, and Missense3D. The structural effect of promising VUS was performed with Molecular Dynamics Simulation (MDS) for 100ns using GROMACS. Post-simulation analysis was performed with Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF), and Radius of gyration (Rg).
Results: We obtained a diagnostic yield of 41.2% (40/97) and identified 67% (65/97) of VUS from WES analysis of probands with DEE. By performing *in silico* analysis, the *de novo* VUS, c.A434C:p.Y145S, was re-classified as a promising VUS. The RMSD, RMSF, and Rg analysis of wild-type *STXBP1* and its mutant form showed that the mutation affects the protein structure stability, residual fluctuation, and compaction.
Conclusion: The real behavior of wild-type protein and its mutant form in their environment was reproduced with MDS. This study would establish a structural and functional characterization pipeline for reclassifying the VUS identified from the WES of DEE.

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The clinical and genetic spectrum of *TRIO*-gene related neurodevelopmental disorder

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Purpose: Heterozygous variants in the *TRIO* gene cause a neurodevelopmental disorder with intellectual disability, behavioral problems and epilepsy. Pathogenic missense variants have been reported in two of the five functional domains in the TRIO protein: the spectrin repeats and GEF1. Genotype-phenotype correlations regarding variant position, head size and degree of intellectual disability (ID) have been suggested. We wanted to delineate the phenotype and investigate if the known genotype-phenotype correlations could be extended.
Method: Thirty patients with pathogenic *TRIO* variants were recruited through an international collaboration.
Results: Seventeen patients had missense variants (8 in the spectrin repeats, 7 in GEF1, 2 in GEF2) and 13 harbored truncating variants. The patients suffered from a spectrum of neurocognitive disorders, ranging from normally developed individuals with ADHD to patients with severe ID and drug-resistant epilepsy. Severe ID was primarily observed in patients with *de novo* variants in the spectrin repeats, whereas truncating variants primarily caused learning disability or mild ID (83%).
Twelve patients (40%) had epilepsy which was drug-resistant in 4 (25%). Generalized and focal epilepsy was reported. Seizure onset was typically between 6 month and 5 years (92%). Structural brain malformations were seen in 62% of the patients: gray matter changes more often in GEDF1 (60%) than in spectrin repeat patients (17%). Micro- or macrocephaly could be predicted by the position of the missense variants in either the GEDF1 or the spectrin repeats. We found two *de novo* missense variants in the GEDF2 domain which has not been previously reported. These two patients had a disorder resembling *TRIO*-associated neurodevelopmental disorder, except they were normocephalic.

Conclusion: All patients had a neurodevelopmental disorder, but the degree of morbidity varied greatly, ranging from mild learning disability to severe developmental and epileptic encephalopathy. The results suggest an extended genotype-genotype correlation including truncating variants and several clinical symptoms.

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The association of rs1800497 gene *DRD2* with levetiracetam-induced psychiatric adverse events

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Purpose: To study associations of polymorphisms of dopaminergic neurotransmission genes (rs1800497 of the *DRD2* gene) with levetiracetam-induced psychiatric adverse events (PAE) in patients with epilepsy (PE).
Method: 79 adults PE taking levetiracetam for a long time (more than 1 year) were examined. The sample consisted of 48 women (66.7%), 24 men (33.3%). Depending on the single-nucleotide variants (SNVs) of the genes, groups were identified: 1st group - genotypes with inclusion of the minor T allele - CT and TT (cytosine/thymine, thymine/thymine), 2nd group - homozygous genotype for the major allele - CC (cytosine/cytosine).
Results: During the study, when analyzing the spectrum of levetiracetam - induced PAE, patients most frequently noted: anxiety 47.2 (%), irritability 43 (%), impulsivity 38.8 (%). There are no correlation between the presence of PAE and daily dose of levetiracetam was found ($p>0.05$). The analysis of association of SNVs rs1800497 genotypes of the *DRD2* gene with PAE, we found: the severity of PAE was greater in the 1st group than in the 2nd group ($p<0.05$). According to the results, anxiety (34.7%, 25 patients), irritability (30.5%, 22 patients), impulsivity (33.3%, 24 patients) are associated with the carriage of the T SNVs allele rs 1800497 of the *DRD2* gene.
Conclusion: Results of the study, there was no dose-dependent effect of the levetiracetam-induced PAE development. The analysis revealed a correlation between the occurrence of certain genotypes and PAE, which suggests the promise of further study of genotyping in epileptology. Carriage of the T SNV allele rs1800497 of the*DRD2* gene is probably one of the predictors of the development of levetiracetam-induced PAE.

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What helps with the unknown: the role of next generation sequencing in infantile spasms syndrome

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Purpose: To investigate the spectrum of genetic etiology in infantile spasm syndrome in relation to genetic testing with an emphasis on next generation sequencing.
Method: A consecutive cohort of patients with infantile spasm syndrome (ISs) were prospectively enrolled in a ISs registry and examined with standard of care procedures since 2008. Patients with unknown etiology underwent next (generation sequencing clinical whole exome sequencing) for further analysis. Seizure and developmental outcomes at last follow-up were reported.
Results: Genetic etiology was present in 28% (68/240). In 10.4% (25/240) of patients with genetic etiology, only further analysis identified genetic diagnosis. Pathogenic variants included *ABAT* in n= 1, *ALG13* in n= 1, *AP3B2* in n= 1, *ATP1A3* in n= 1, *CEP170B* in n= 1, *CSNK2B* in n=1, *COL4A1* in n=1, *GABBR2* in n=2, *KAT8* in n= 1, *KCND2* in n=1, *KCNH1* in n=1, *KCNT1* in n=2, *KCNQ2* in n= 2, *POGZ* in n=1, *PPP3CA* in n= 1, *SCN2A* in n=2, *SLC9A6* in n= 1, *SLIT3* in n=1,

SRPX2 in n=1, *TSC1* in n=1, and *UFC1* in n= 1- by WGS).
Wes trio sequencing showed no pathogenic variants in further 10% tested.
Conclusion: Genetic etiology is present in 28% all patients, in 10% only next generation sequencing revealed a rare genetic etiology, which is important for further and early treatment plans. Still in 10%, next generation sequencing of unknown etiologies did not identify any pathogenic variant. Accurate and timely next generation sequencing genetic testing is therefore most relevant for early and individually targeted treatment. Further studies and international registries are needed as single cohorts do identify only single patients with rare diseases in infantile spasm syndrome.

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KCNA2 mutation responsible for the genetic picture of epilepsy, first description in South America

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Purpose: KCNA2 is a voltage-gated potassium channel that mediates the transmembrane transport of potassium in excitable membranes, mainly in the brain and central nervous system, but also in the cardiovascular system. It prevents aberrant action potential firing and regulates neuronal output. It forms potassium-selective tetrameric channels through which potassium ions pass according to their electrochemical gradient. The channel alternates between open and closed conformations in response to the voltage difference across the membrane (PubMed:19912772, PubMed:8495559, PubMed:11211111, PubMed:23769686). It can form functional homotetrameric channels and heterotetrameric channels that contain variable ratios. Its association with epilepsy of genetic origin is scarce and reports in South America do not exist.
Method: PCR genetic sequencing was performed to identify mutations in a patient with a form of generalized epilepsy that is difficult to control.
Results: A mutation was found in the KCNA2 gene, it would be the first report in the South American scientific literature since the reports in the search engines are null so far.
Conclusion: We recommend carrying out more extensive genetic studies in order to characterize the genetic forms of epilepsy that have not been characterized in our environment. The family group is being followed up to identify related genetic alterations.

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Glut1-deficiency syndrome with extreme phenotypic variability in a five-generation

family carrying a novel SLC2A1 mutation

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Purpose: GLUT1 deficiency syndrome (GLUT1ds) is a heterogeneous metabolic disorder due to the reduced expression of GLUT1, a glucose transporter of central nervous system. GLUT1ds is caused by mutations in the SLC2A1 gene inherited as an autosomal dominant trait, even if most detected SLC2A1 mutations arise de novo. Growing evidence has illustrated that the clinical spectrum of GLUT1ds is broader. Here, we report a five-generation Italian family with heterogeneous phenotypes consistent with milder GLUT1ds related to a novel heterozygous missense mutation of SLC2A1 gene.
Method: We present clinical and genetic features of a large five-generation Italian family.
Results: The family included 14 affected members with mild heterogeneous phenotypes, including isolated mild cognitive impairment (3/14), behavioral disturbances (5/14), epileptic seizures (9/14) and gait disabilities (1/14). Notably, brain MR depicted hippocampal sclerosis in the 8-year-old proband who also had drug-responsive absence seizures associated with attention-deficit-hyperactivity disorder. His 52-year-old father, who had self-limited occipital epilepsies of childhood, developed a mild spastic paraparesis related to a reversible dorsal myelitis. The CSF analysis revealed a glucose ratio below 0.45. Molecular study revealed a novel heterozygous variant (c.446C>T) in exon IV of SLC2A1 that was found to co-segregate with the illness. This variant causes an amino acids substitution (p.Pro149Leu) at the fourth transmembrane segment (TM4) of GLUT1, an important domain located at the catalytic core of the protein. Many prediction programs predicted that this variation had deleterious effect.
Conclusion: Our study illustrates the extremely heterogenous phenotypes in familial GLUT1ds, ranging from milder classic phenotypes to more subtle neurological disorder including paraparesis. Most important, we identified a novel SLC2A1 pathogenic variant (c.446C>T), providing new insight into the pathophysiology of GLUT1ds. The extreme heterogeneous phenotypes of family members carrying the same mutation indicates that secondary genes and other modifying factors may modulate the expression level of GLUT1.

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Uncovering the multi-omic single-nuclei landscape of hippocampal sclerosis type I from patients with mesial temporal lobe epilepsy: clues into mechanism

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Purpose: Introduction/objectives: We aim to construct a compressive map of molecular interactions occurring in tissue obtained by epilepsy surgery of patients with pharmacoresistant mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE+HS) using single-cell/nuclei omics techniques. Furthermore, with this approach, we can identify the molecular pathways activated in different cell populations and understand better how the cells' epigenome landscape may change over time.
Method: Materials and Methods: We selected 14 samples from patients with MTLE+HS and classified them as type I hippocampal sclerosis by post-surgical pathological examination. Samples were divided into three groups according to disease duration (DS): Group 1: DS≤25 years (n=3); Group 2: 26 years≤DS≤39 years (n=5); Group 3: DS≥40 years (n=6). In addition, neuronal cell nuclei were isolated, resulting in 28 multi-omic libraries (14 Single Nuclei ATAC + 14 Single Nuclei Gene Expression; 10X Genomics Multiome Protocol).
Results: To date, our results identified 16 clusters of different cell populations, with a median of 1.038 GEX/cell and 96.090 peaks corresponding to genomic regulatory regions of open chromatin. Furthermore, we obtained a total of 75,445 cells aggregating all samples. The identification of different cell types, expression gene patterns, and regulatory elements is underway.
Conclusion: To our knowledge, this is the first study applying a single-nuclei multi-omic approach focusing on studying molecular changes occurring over time in tissue from patients with MTLE+HS. We obtained high-quality sequencing data from more than 70.000 single cells and identified 16 different cell sub-populations from the sclerotic hippocampi of patients. Our work may contribute to a better understanding of disease changes over time, especially in identifying key activated molecular mechanisms, changes in gene expression regulation, and the overall epigenome landscape at different disease time points in patients with MTLE-HS.

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DLG4-related synaptopathy: expanding the genotypic and phenotypic spectrum

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Purpose: *DLG4* encodes PSD-95, fundamental for the organization of the post-synaptic density (PSD), a dynamic network responsible for the modulation of strength and plasticity of the glutamatergic synapses. *DLG4*-related synaptopathy was recently described, characterized by intellectual disability, autism spectrum disorder features, ADHD, epilepsy and hypotonia[1]. The aim of this study was to define and expand the phenotypic and genotypic spectrum of DLG4 synaptopathies in a large cohort of affected patients.
Method: Data on unpublished and published cases were collected through EpiCare, ERN ITHACA, GeneMatcher and SHINE syndrome (*DLG4*-related synaptopathy) foundation (shinesyndrome.org). Data on clinical, genetic, neuroimaging, and neurophysiologic features were obtained.
Results: The cohort comprised of 66 patients, including updated data of 17 already published individuals. Main clinical features included intellectual disability (98%), sleep disturbances (60%) and neurologic symptoms such as hypotonia (64%). Onset of encephalopathy usually around the first year of life. A variety of dysmorphic features were detected in more 60% of subjects. Thirty-one patients (47%) developed epilepsy with focal, generalized tonic clonic, absence, tonic, myoclonic seizures and/or epileptic spasms. Mean age at epilepsy onset: 6,2 years. EEG showed generalized, multifocal, and focal epileptic abnormalities. Nine (37,5%) individuals showed an ESES-like EEG pattern. Heterogenous MRI findings (including anomalies of the corpus callosum, brain atrophy, white matter hyperintensity) were observed in about 30% of subjects. Eleven (44%) epileptic patients were seizure free at the last evaluation. We found 50 different pathogenic variants, 30 not previously reported; most of them were protein-truncating variants. No genotype-phenotype correlation was found.
Conclusion: The DLG4-related synaptopathy is a developmental and epileptic encephalopathy, with onset within the first year of life. Almost half of the patients are epileptic with different seizure types; around 50% achieved seizure freedom. We could not observe any genotype-phenotype associations.

1. Rodríguez-Palmero, A. et al. Genetics in Medicine, 2022. 23, 888–899

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Adult-onset epilepsy in cardiofaciocutaneous syndrome with *MAP2K1* mutation

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Purpose: Cardiofaciocutaneous syndrome (CFCS) is a rare genetic disorder presenting with congenital heart defects, craniofacial dysmorphism, and skin abnormalities. The patients with

CFCS often had neurologic abnormalities including intellectual disability and epilepsy. Regarding epilepsy in CFCS, there is limited information about symptomatic characteristics and therapeutic strategies. Here we analyzed clinical features of a CFCS patient who developed adult-onset epilepsy.
Method: We retrospectively analyzed the long-term clinical course of a 45 years-old woman with genetically confirmed CFCS carrying a *MAP2K1* mutation. The patient presented psychomotor delay from infancy and had severe intellectual disability. At 30 years of age, she developed generalized convulsion which was difficult to treat due to drug-induced hypersensitivity syndrome.
Results: She showed three types of seizure semiology; generalized tonic-clonic seizure, head version to the right followed by right-dominant convulsion, and loss of awareness. Interictal EEG showed poorly organized posterior dominant rhythm in 8-9 Hz, generalized slow generalized and multifocal independent activities, and generalized and multifocal independent epileptiform discharges, suggesting combined generalized and focal epilepsy. Phenobarbital caused drug-induced hypersensitivity and discontinued. Valproate was effective to generalized convulsion but caused appetite loss. Levetiracetam was effective to all seizure types but irritability and insomnia appeared. Lacosamide was effective without adverse events. Her refractory epilepsy was finally controlled with a combination of valproate, levetiracetam, and lacosamide. At 45 years of age, we reached a diagnosis of CFCS by whole genome sequencing that revealed a pathogenic *MAP2K1* mutation.
Conclusion: In patients with CFCS, the onset of epilepsy is common in childhood, thus little is known about adult-onset epilepsy and its prognosis. The present case provides detailed information about clinical course and treatment of epilepsy according to the diagnosis of combined generalized and focal epilepsy, which may be useful for optimal treatment and prognostic prediction in CFCS.

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Neurological phenomenology of the IRF2BPL mutation syndrome

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Purpose: IRF2BPL is an intronless gene that was mapped to 14q24.3 chromosome and codes for the interferon-regulatory-factor-2 binding like protein. We analysed the clinical characteristics of the patients reported in the literature and of one additional patient we observed in order to better delineate the phenomenological spectrum of the disease.
Method: A review of the literature was performed using Pubmed and the following key

words: IRF2BPL gene; EAP1 gene; c14orf4 gene. Our search identified 10 papers, published in English from 2018 to 2021, that provided clinical details of 27 patients carrying IRF2BPL To these is added a further case identified in our hospital, with slightly atypical characteristics compared to most of the others already published.
Results: We referred to the number of neurological domains (epilepsy, dystonia, ataxia, spasticity, and ocular disturbances) that were associated with developmental delay/regression as a surrogate of the clinical severity of IRF2BPL-related disorders. Spearman correlation analysis suggested a significant positive correlation between the number of affected neurological domains and the presence of MRI abnormalities (rho = 0.45, p = 0.02), while no significant correlation emerged between the number of affected clinical domains and age at disease onset (rho = 0.18, p = 0.35) or variant type (rho = 0.30, p = 0.12).
Conclusion: Our analysis highlights that the IRF2BPL mutation syndrome is highly specific to the central nervous system, as witnessed by the almost constant association with developmental delay/motor regression, the relatively high frequency of a variety of neurological symptoms that could be attributed to at least five neurological domains (epilepsy, dystonia, ataxia, spasticity, and ocular disturbances), and the low frequency of multi-organ involvement. Diagnostic work-up in the adult patients should consider the clinical picture of the IRF2BPL mutation syndrome herein delineated and the existence of conditions that shares developmental delay/regression and may result from acquired/genetic or unidentifiable underlying etiology.10.1016/j.seizure.2022.04.010

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Epilepsy and white matter disorders: a case report and literature review

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Purpose: The evidence for the association of white matter disorder and epilepsy is scant and unclear.
Method: Therefore, we aim to report an illustrative case and carry out a literature review that allows an adequate approach to the association of these diseases.
Results: A 39-year-old Colombian male, spanish professor, who developed epilepsy at the age of 14 years. A white matter disorder was documented in brain MRI, with bilateral parieto-occipital pattern unchanged over time. Metachromatic leukodystrophy and X-Linked adrenoleukodystrophy were ruled out, as well as other mitochondrial and peroxisomal diseases. The history and clinical evolution did not suggest neonatal hypoglycemia nor Krabbe disease. At 38 years of age, he began with difficulty climbing stairs and rowing. On neurological examination with limb-girdle muscular weakness. Finally, a whole-exome-sequencing reported a mutation in gene LAMA2, which has been associated with muscular dystrophy, epilepsy, and white matter lesions (Salvati A.Seizure. 2021 Oct; 91:425-436).
Although it is true that the cerebral cortex plays a fundamental role in epileptogenesis, evidence of other sources of epileptogenicity has become clearer over time. The role of the brain stem and thalamocortical networks in the disease is known, in some cases, as the

source of seizures (Hogan RE. Epilepsy Curr. 2020;21(1):27-294). Additionally, in the approach of epilepsy and white matter lesions specially extensively spread lesions, as in this case, it's important to evaluate clinical characteristics and to identify the pattern of the compromise of white matter and rule out etiologies as metabolic, inflammatory, toxic and radiogenic causes. Also, when white matter changes are symmetrical is recommended to study genetic etiologies (Weidauer. Rofo Dec 2020;192(12):1154-73)
Conclusion: The characterization of clinical features, the evolution and the pattern of white matter involvement will suggest the possible etiology of the clinical picture.

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Navigating through SCN8A-related epilepsy: a new genotype phenotype description requiring a long-term treatment with high levels of carbamazepine

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Purpose: Description of the clinical presentation, diagnosis, long term follow-up and treatment of a patient with SCN8A-related epilepsy to highlight a new genotype-phenotype and reflect on the treatment with sodium channel blockers.
Method: We report a 16-year-old boy with focal seizures triggered by fever and early onset (4 months). He had normal cognition and psychomotor development and no motor disorder. Genetic testing revealed a de novo variant c.5615G>A of the SCN8A gene (p.Arg1872Gln), classified as pathogenic. Treatment with Carbamazepine was ultimately successful and a correlation was observed between seizures' recurrences and reduction in Carbamazepine blood levels.
Results: The clinical presentation of the patient could be suggestive of several developmental and epileptic encephalopathies, mainly Dravet syndrome or other channelopathies. Genetics may help to personalized therapy, for instance Na sodium channel blocker, that are contra indicated in DS at this age. The patient's clinical presentation does not fully fit in a reported phenotype (benign/intermediate and severe). In addition, our prediction of prognosis was challenging. The patient de novo variant is reported in the literature in association to severe phenotype (early onset, associated with drug resistance, severe intellectual disability, motor regression) although he had a good outcome. This highlighting the need for further research to better understand the complex relationship between genetic variants, their functional effect and the clinical phenotypes in SCN8A-related epilepsy. In this case, there was a clear need to maintain carbamazepine about the mean therapeutic range in order to avoid seizures recurrence, mainly in febrile context.
Conclusion: This case report highlights the importance of genetic testing in the diagnosis and

targeted treatment of SCN8A-related epilepsies and the potential usefulness of sodium channel blockers and the still needed markers for a phenotype-genotype correlation.

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The importance of variants of uncertain significance in genetic epilepsy diagnosis and management in children- experience from a tertiary care center

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Purpose: More than 900 epilepsy-associated genes have been described so far in the literature, with rapid advances. Epilepsy genes play an important role in neuronal excitability, cortical development or synaptic transmission and their identification offers a sometimes long-awaited response for the patients and families involved. Apart from clearly pathogenic, known mutations, variants of uncertain significance (VUS) often arise when performing genetic testing in epilepsy patients.
Method: We present a retrospective longitudinal study on the genotypic and phenotypic correlations in pediatric epilepsy patients with VUS identified after genetic testing. The study was performed in a tertiary care , rare disease center, between 2016- 2022.
Results: In approximately 40% of the patients included, the phenotype was suggestive for a precise genetic etiology- eg. KCNT1, PTEN, SCN1A, SLC2A1, etc.
Conclusion: We emphasize the importance of close collaboration between epileptologists and geneticists when approaching an epilepsy patient with a probable genetic diagnosis. Moreover, early identification and correlation could have a great impact on quality of life and seizure management.

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IRF2BPL as a novel causative gene for progressive myoclonus epilepsy

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Purpose: Variants in *IRF2BPL* have been recently described as a cause of neurodevelopmental disorders with multi-systemic regression, epilepsy, cerebellar symptoms, dysphagia, dystonia, and pyramidal signs. We describe a novel *IRF2BPL*-related phenotype consistent with progressive myoclonic epilepsy (PME).
Method: We collected the electro-clinical and genetic data of three unrelated subjects and reviewed the features of the 31 previously reported subjects with *IRF2BPL*-related disorders.
Results: Our three probands (aged 28-40 years) had drug-resistant epilepsy with severe light-induced and action myoclonus, as well as cognitive, speech, and cerebellar impairment. These symptoms had onset around puberty and progressively worsened over time, in keeping with typical PME. The EEG/EMG-polygraphic recordings showed rhythmic myoclonic jerks involving synchronously agonist/antagonist muscles, time locked with spike/polyspikes-and-slow-waves predominant in the fronto-central regions. The skin biopsy revealed intracellular Lafora body-like inclusions in one subject. All three subjects harbored *de novo* non-sense variants (c.364C>T; p.Gln122*and c.370C>T, p.Gln124*, respectively) in a highly conserved region of the *IRF2BPL* gene.
From the critical review of the literature, it emerged that 11/31 previously reported cases presented with myoclonic epilepsy and progressive neurodegenerative symptoms, partially overlapping the phenotype of our patients. Since the age at symptom onset and the rate of *IRF2PL*-disease progression can vary, this raises the suspicion that a number of previously reported cases might be unrecognized PME or might have developed PME later in life.
Conclusion: Our data indicate that *IRF2BPL* has to be considered a novel causative gene for PME. The IRF2BPL protein acts as an E3 ubiquitin ligase; its dysfunction may lead to a lysosomal storage disorder. This suggests a possible common pathogenic pathway between *IRF2BPL*-PME, Lafora disease, and other storage disorders-PMEs. Since the prognosis and outcome of PMEs depend on their specific etiology (still undetermined in 28% of the cases), our results may contribute to a better understanding and treatment of the disease.

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The changing landscape of genetic testing in paediatric neurology – a retrospective review of genetic testing in a large tertiary centre

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Purpose: A broader understanding of genetic aetiology and increasing access to investigations has allowed for effective precision diagnosis and treatment of early onset paediatric neurological conditions, including early onset epilepsy (Byrne et.al 2021). This allows for positive patient outcomes but an increased workload for the paediatric neurology and genetic teams (Ritter et al, 2020). We aim to understand the landscape, outcome and cost of genetic testing for paediatric neurology patients in a large tertiary centre. This is an interim report with pro-

visional data (full data will be available from IEL meeting).
Method: The period of study ranges over 5 years from Jul 2017 to July 2022. A retrospective analysis of all genetic testing sent by the paediatric neurology consultants is being reviewed. Anonymised patient data regarding genotype and phenotype was collected include test type and year. The cost of testing will use an estimated price then totalled per patient.
Results: Our provisional result have identified patients of four paediatric neurology consultants working within CHI Crumlin during the specified period.
1294 genetic investigations were ordered and sub analysis to exclude parental samples revealed this represented 597 patients. There were 860 molecular investigations and 434 cytogenetic investigations.
By year there were 265 genetic investigations in 2022 (6 months = estimated 530/year), 2021=297, 2020=124, 2019=187, 2018=307, 2017=114 (6 months = estimated 228/year).
Early analysis shows 24% of patients received a genetic diagnosis. An additional 12% had variants of uncertain significance.
78 patients had exome sequencing performed; 59 trio-exome, 13 singleton and 6 duo-exome (74% completed since 2022).
Conclusion: The study has shown an apparent decrease in testing during the COVID 19 pandemic in 2020 but subsequently an increased uptake of genetic testing within the department. Our future data will be used to calculate the cost and analyse if there is a shift in testing type since 2017.

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Epileptic encephalopathy due to ATP1A2 gene mutation: clinical characteristics associated with three variants

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Purpose: The development of molecular studies has allowed the identification of the genetic cause of various diseases such as infantile epileptic encephalopathy.
The mutation in the ATP1A2 gene, which encodes the alpha 2 subunit of the Na+/K+-ATPase, has a broad clinical spectrum that can range from familial hemiplegic migraine to early onset epileptic encephalopathy, which is important to identify due to the multiple comorbidities it presents, the psychosocial impact that it could cause in patients and their families, and the therapeutic studies that are being carried out with NMDA receptor antagonists.
We aimed to describe the manifestations of early onset severe ATP1A2-related epileptic encephalopathy, and its underlying mutations in a cohort of three patients.
Method: A retrospective review of the medical records of a cohort of 3 patients was performed.
Results: Patients (ages from 6 months to 10 years) had onset of symptoms at an early age (5 days to 2 years). Common clinical characteristics were found: global neurodevelopmental delay with subsequent intellectual disability, drug-resistant epilepsy, and recurrent status

epilepticus. All had variants of the ATP1A2 gene (ATP1A2 c. 720_721del (p.Ile240MetfsTer9), ATP1A2 c.30222C>T (p.G366C), ATP1A2 c. 1096. G >T (p.Arg1008Trp)) reported as pathogenic according to the ACMG. Memantine was administered to one of the patients, currently under follow-up for efficacy evaluation.
Conclusion: The new genetic evidence reported here strengthens the gene–disease relationship since it is estimated that ~5% of ATP1A2 mutations may be associated with severe and novel phenotypes that could be related to epileptic and developmental encephalopathies, as in the case of our patients. Prospective studies are required to evaluate not only the phenotype but to assess the efficacy of new therapies with NMDA receptor antagonists in reducing seizure frequency, with subsequent improvement of quality of life.

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Uridine-responsive epileptic encephalopathy: precision treatment across the age spectrum

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Purpose: Uridine-responsive epileptic encephalopathy, or CAD deficiency, is a disorder of *de novo* pyrimidine synthesis due to biallelic pathogenic variants in *CAD*, associated with developmental delay, movement disorder, epilepsy and dyserythropoietic anaemia. We describe 4 patients presenting from the neonatal period into adulthood.
Method: Case note review.
Results: Patient 1, now 9-months-old, presented with microcephaly and seizures from day 8 of life evolving into pharmacoresistant epileptic spasms. She developed spastic quadriplegia, dyskinesia and bulbar dysfunction. Trio whole exome sequencing (WES) found compound heterozygous variants in *CAD*. Uridine replacement using uridine monophosphate (UMP) resulted in improved dyskinesia and seizure control.
Patient 2, now 21-months-old, presented with refractory status epilepticus at 3 weeks of age. Trio WES revealed compound heterozygous variants in *CAD*, one novel and one previously

reported. UMP treatment within 2 days of genetic diagnosis resulted in seizure cessation. Patient 3, a 15-year-old male, presented with learning difficulties, language impairment, pharmacoresistant focal epilepsy from 2.5 years, progressive cerebellar ataxia from late childhood with loss of ambulation, and dysarthria. Neuroimaging revealed progressive cerebellar atrophy. Trio whole genome sequencing at 14 years revealed biallelic pathogenic variants in *CAD*. After 3.5 months of UMP therapy, he became independently ambulant with significantly improved seizure control.
Patient 4 is a 21-year-old female with mild learning difficulties and generalised seizures from adolescence controlled with monotherapy. At 21 years, she developed refractory status epilepticus whilst pregnant. Urgent trio WES revealed compound heterozygous pathogenic variants in *CAD*. After 10 days of UMP treatment, she became seizure free.
All patients demonstrated wide red cell distribution width and abnormal blood films with anisocytosis or anisopoikilocytosis which improved with UMP therapy.
Conclusion: CAD deficiency represents a treatable neurological disorder. Requesting FBC/blood film in patients with drug-resistant epilepsy associated with co-morbidities is key to diagnosis. Earlier genomic testing would permit timely targeted treatment and improved outcome.

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CARS2 associated status epilepticus in early childhood

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Purpose: A 15 month old girl, with a normal perinatal and infantile history, presented to us with generalized refractory status epilepticus. Upon evaluation, she had similar history of seziures in her elder sister, and three maternal cousins, all of them had febrile status epilepticus between 15-18 months of age and subsequently expired. She was managed aggressively for status epilepticus as per the protocol, with investigations for underlying familial status epilepticus. Whole exom sequencing showed that in addition to the known pathogenic variant in exon 6 of the *CARS2*(NM_024537.4), we found an additional c.194del(p.Leu65GlnfsTer40) variant in Exon 1, that is not previously reported in the literature, till date.
Method: Laboratory investigations including thyroid function, blood gas analysis, serum lactate level and liver function tests were within normal limits. Ultrasound abdomen revealed normal size and architecture of the liver. The metabolic parameters including the amino acids were within normal limits. MRI of brain revealed no significant pathology. Genetic testing showed compound heterozygous mutations of the CARS2 gene which were identified by whole exome sequencing.
Results: Whole genome exom sequencing showed compound heterozygous mutation in CARS2 gene that included -the missense c.655G>A(p.Ala219Thr) variant in Exon 6 and the frameshift c.194del(p.Leu65GlnfsTer40) variant in Exon 1.
Conclusion: The frameshift c.194del(p.Leu65GlnfsTer40) variant in Exon 1 of CARS2 gene has not been reported previously as a pathogenic variant, nor a benign variant, to our knowledge. The p.Leu65GlnfsTer40 variant has been reported with allele frequency of 0.0008% in

gnomAD Exomes and is novel (not in any individuals) in 1000 Genomes. However, additional functional studies are required to prove the pathogenicity of this variant.

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Genome-wide association study of epilepsy in the Danish iPSYCH cohort – a study of genetic correlation with previous findings

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Purpose: Although the genetic component of epilepsy has been estimated to be substantial (25-70%) in twin studies, its genetic architecture remains relatively unexplored. Recent GWAS have identified several novel loci implicated in specific epilepsy subtypes and estimated the heritability explained by common variants to be 17.7% (95% CI 15.5 - 19.9%) (Berkovic et al., 2022). In this study we use the Danish iPSYCH case-cohort sample to investigate the genetic architecture of epilepsy and comorbidity with psychiatric disorders.
Method: Initially, a GWAS was conducted using the Danish iPSYCH cohort consisting of 3.961 epilepsy cases and 41.609 controls after filtering. Genetic correlations between the resulting effect sizes and those of Berkovic et al., 2022 were estimated using LD score regression, and the heritability explained by common variants was estimated with individual-level data using Genome-wide Complex Trait Analysis. Further iterations of these analyses were performed with a filtered phenotype, where cases diagnosed before the age of 3 were removed and later also cases with only a single epilepsy diagnosis.
Results: The estimated genetic correlations were non-significant ($P > 0.05$), irrespective of epilepsy phenotype used. Using externally trained polygenic scores for epilepsy, we did however identify significant association with epilepsy in the iPSYCH data, suggesting some shared genetic component. The estimated heritability explained by common variants was similarly small as it was estimated to be 4.94% (95% CI 2.74 - 7.13%) in the unfiltered phenotype.
Conclusion: These results suggest a large discrepancy between epilepsy cases in the iPSYCH data and the Berkovic et al. study, which we speculate could be due to the majority of the epilepsy cases considered having a comorbid psychiatric disorder. This suggests a need for validation of the epilepsy diagnosis in the Danish register and a more specific classification of individuals for more effective subdivision of the phenotype.

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MBOAT7-encephalopathy: characterizing the epileptology

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Purpose: MBOAT7-encephalopathy is described in 50 patients and symptoms include global developmental delay, psychiatric and behavioral comorbidities, movement disorders and epilepsy. Although, 25/50 had seizures, the epileptology remains ill-defined. We aim to present the epileptology of MBOAT7-encephalopathy.
Method: We recruited 12 patients with biallelic MBOAT7 variants and obtained clinical data regarding age at seizure onset/offset and semiology, development, medical history, examination, electroencephalogram, neuroimaging, and treatment. Seizure and epilepsy types were classified based on ILAE guidelines.
Results: Twelve patients were identified with a mean age of 13 years. Nine patients experienced seizures with an average age of seizure onset at 36 months (range 2 – 81 months). 7/9 (63%) only had generalized seizures, while 2/7 had focal motor seizures with impaired awareness. Three had febrile seizures, and two experienced status epilepticus. 8/9 were diagnosed with developmental and epileptic encephalopathy, while 1/9 had intellectual disability plus epilepsy (ID+E). Half became seizure-free, often with a combination of sodium channel blockers, levetiracetam, valproic acid, ethosuximide, and/or topiramate. Anti-seizure medications that seemed to be beneficial in some patients were ineffective or exacerbated seizures in others One patient was implanted with VNS, one had a callosotomy, and three had ketogenic diet; with significant improvement on seizure burden. We obtained 25 EEG reports taken between the 8th day and 13th year of age; 73% had normal background activity, and 27% had either a focal or a generalized slowing. Half showed generalized slow-wave, 20% had multifocal interictal epileptic discharges (IEDs), and 20% had focal IEDs in the parasagittal region.

Conclusion: MBOAT7-encephalopathy is a complex autosomal recessive disorder associated with a wide spectrum of epilepsy phenotypes, and half of the patients experience seizures that can be treatable. There are no definitive EEG patterns.

1143

Clinical and genetic characteristics of early onset developmental and epileptic encephalopathies

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Purpose: Evaluation of clinical and genetic data of patients with neurodevelopmental disorders and the onset of epileptic seizures up to 18 months of age
Method: The work included a clinical, EEG, MRI and genetic data from 200 patients aged 10 months to 5 years, obtained as a result of examination of patients with neurodevelopmental disorders and the onset of epileptic seizures up to 18 months of age, observed from 2015 to 2020 in the Veltischev Research and Clinical Institute of Pediatrics and Pediatric Surgery of the Pirogov RNRMU and medical center "Genomed", Moscow, Russia.
We performed a multi-gene panel (1089 genes), WES and WGS using Illumina NextSeq 500 and in-house analysis software.
This work was granted by RSCF № 22-14-00395.
Results: Pathogenic mutations in 45 genes responsible for developmental encephalopathies and/or epileptic encephalopathies were found in 126 (63%) patients. The channelopathies group included 61 patients who were diagnosed with 12 genetic variants caused by mutations in the *ATP1A3, CACNA1A, GABRA1, GABRB2, GABRB3, KCNA2, KCNB1, KCNQ2, KCNT1, SCN1A, SCN2A, SCN8A* genes; there were 16 patients in dysregulation of transcription and translation group: *CDKL5, CHD2, CUX2, EEF1A2, FOXG1, GNAO1, IRF2BPL, KANSL1, KIAA2022, MEF2C;* 16 patients in dysregulation of synaptic processes group: *DNM1, PRRT2, STXBP1, SYNGAP1;* 16 patients in impaired cell growth and differentiation group : *PAFAH1B1, PCDH19, PPP3CA, SMC1A, TBC1D24, TSC2, NF1, WDR45;* 11 patients in group of impaired transport and metabolism of small molecules within and between cells: *DYNC1H1, MFSD2A, SLC2A1, SLC6A5*, *SPTAN1;* 6 patients in neuronal metabolism group: *ADSL, ALG1, ASNS, GMPPB, ITPA, PIGA.*
Conclusion: Early onset of seizures (up to 5.7 months) and combination of the following clinical symptoms increased the detection of genetic causes: febrile seizures, slowing of background activity on the EEG, regional accentuation of epileptiform activity on the EEG, diffuse muscle hypotonia and autism (ROC analysis with AUC equal to 0.824).

1150

DEPDC5 gene mutation: variety of clinical manifestations and treatment, familial cases

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Purpose: Mutations in the DEPDC5 gene can cause various seizure disorders known as familial mesial temporal lobe epilepsy and infantile spasms.

Method: We observed 2 families in which seizures debuted at different times, had different clinical manifestations, where a mutation in the DEPDC5 gene was detected.
Results: In the first family, both father and son have epileptic seizures. Fathers focal seizures began at the age of 12 years old, they were frequent, focal, resistant to therapy, MRI is normal. Now he has seizures. Son had tonic convulsions from 10 days of life, after the appointment of FB, the seizures were stopped, from 6 months had started infantile spasms, stopped with combination of VGB and VPA, from 10 months of age he has a frequent focal seizures, severe developmental delay, pronounced hemiparesis. MRI showed focal cortical dysplasia. Therapy included various drugs. At the age of 4 years, surgical treatment was performed; there were no seizures after the operation. Father and son have pathogenic variant of gene DEPDC5 (Gain (exons 5-7) copy number =3)).
In the second family father and 2 daughters had seizures. Father had focal seizures until the age of 10 years and did not receive drags. The eldest daughter had seizures from the age of 5 years old, initially diagnosed Rolandic epilepsy. She took CBZ, after 3 years repeated frequent attacks, resistant to therapy, the best combination now: STM and CBZ. Younger girl had focal seizures after 10 years old. She took TPM, no seizures now, stopped therapy. MRI of both sisters is normal. Both girls underwent genetic testing: c.364-1G> A (splice acceptor) – heterozygous – likely Pathogenic.
Conclusion: The clinical picture was different even within the family in the presence of the same genetic changes. Therapy was also different. The pathology of the gene DEPDC5 is variable.

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Epilepsy in succinate semialdehyde dehydrogenase defect

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Purpose: We aimed to characterize epilepsy in two adult patients with defective succinate semialdehyde dehydrogenase due to mutations of the ALDH5A1 gene
Method: We analysed the electro-clinical features and the epilepsy course.
Results: The youngest patient (female 24 years) had psychomotor delay, resulting in severe cognitive disability. She developed generalized seizures at the age 13, sometimes induced by intermittent light stimulation. Some EEGs showed generalized spike and waves abnormalities and photosensitivity at the intermittent photic stimulation. Seizures were easily controlled with levetiracetam. Diagnosis was reached before the onset of the epilepsy based on biochemical and genetic findings.
The oldest patient (male 37 years) diagnosed in infancy with language delay and learning difficulties, manifested a generalized seizure at 17 years, during fever. Thereafter he had sporadic tonic-clonic seizures without fever. However, at the age 34, during a febrile episode, the patient had recurrent seizures leading to convulsive epileptic status (ES) which resulted

difficult-to-treat. Then he had protracted episodes of fluctuating awareness, and behavioral changes, lasting several hours almost daily. The EEG monitoring confirmed the epileptic nature of these episodes, showing rhythmic theta activity mixed with repetitive spikes, prevalent on one side. Seizure decreased with poly-therapy. Diagnosis was lately reached through a genetic panel for epilepsy.
Conclusion: Our observation suggests that the electroclinical picture is not clearly distinctive. Seizures can be well-controlled for long time period. However, clinical condition can suddenly change with ES eventually complicating the clinical picture. Careful monitoring is needed.

1222

The phenotype and genotype spectrum of individuals with ANK3 variants

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Purpose: *ANK3* encodes Ankyrin-G, a protein involved in neuronal development and signaling [1]. Only 23 individuals carrying a pathogenic autosomic dominant (AD) or recessive (AR) *ANK3* variant have been described so far, the most with intellectual disability (ID), language

and motor delay, and behavioral problems. We performed this study to increase the knowledge about this rare disease, to define the phenotypic spectrum and to determine genotype-phenotype correlation of *ANK3* variants.
Method: Through an international network we collected the clinical and genetic information of 18 novel individuals with AD and AR *ANK3* variants and we reviewed the data available for the 23 previously described subjects. Age ranged from 18 months to 45 years (median age at latest evaluation was 7.5 years). Gender ratio was 23 males and 15 females. 32% of them were reported with an *ANK3* homozygous or compound heterozygous variant and 68% with an *ANK3* heterozygous mutation. We identified 11 homozygous/compound heterozygous variants (9/11 missense and 2/11 truncating) and 24 heterozygous mutations (10/24 missense and 14/24 truncating).
Results: In the total cohort the 91% of the subjects available presented with ID, ranging from mild (52%) to moderate (22%) to severe (26%), ASD (74%), behavioral problems (88%), language delay (93%), ranging from no speech/profoundly delayed speech (62.5%) to mildly delayed speech (37.5%), motor delay (75%), hypotonia (60%), epilepsy (38%), and sleep disturbances (48%). In the homozygous/compound heterozygous subgroup epilepsy and sleep disturbances were significantly more represented than in the heterozygous group ($p<0.05$). A more severe phenotype was observed in truncating variants and more severe in homozygous/compound heterozygous mutations.
Conclusion: Our data provide further support for autosomic dominant or recessive *ANK3* variants as a genetic cause for neurodevelopmental disorders, including ID, language and motor delay, ASD and behavioral problems, epilepsy, and sleep disturbances and recognizes a genotype-phenotype continuum spectrum.

1230

Atypical CLN8 related variant late infantile neuronal ceroid lipofuscinoses: two turkish cases

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Purpose: The neuronal ceroid lipofuscinoses (NCLs) comprise a group of progressive neurodegenerative disorders. Clinically, these disorders characterized by seizures, progressive visual loss and mental decline. To date, 14 distinct NCL subtypes have been described. CLN8 mutation was first identified in Finnish patients, and the condition was named Northern Epilepsy (NE). Subsequently, a distinct clinical form of CLN8 was found in Turkish, Italian, and Pakistani patients and named as variant late infantile neuronal ceroid lipofuscinoses (vLINCLs). The vLINCL phenotype generally shows rapid symptom progression, although some have a milder course. All the Turkish cases with vLINCL in the literature have progressive form and non of the vLINCL phenotype patients in the literature presented with febrile seizure.
Method: Herein, we report two cases of vLINCL with milder form in which one of the patients

presented with febrile seizure.
Results: **Cases**
A three years old boy with a homozygous CLN8 mutation: c.610C>T (p.R204C) and A 3-year and 10 months old boy a homozygous CLN8 mutation: c.221G>A (p.Gly74Asp) with vLINCL phenotype were reported.
Conclusion: Our patients have been followed-up for approximately for 3 years and the deterioration course was not rapid. The reason for this discrepancy remains unknown; further large-scale case series are warranted.

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The specific epilepsy phenotype of SRRM2 developmental and epileptic encephalopathy

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Purpose: Due to the recent characterization of the neurodevelopmental disorder associated with SRRM2 loss-of-function variants (Cuinat et al, 2022), we aim to delineate the electroclinical features of patients with *SRRM2* variants.
Method: Cases were identified by an international network of epileptologists/geneticists. Data was extracted for clinical history, examination, electroencephalography (EEG) and imaging.
Results: Of the patients included, four females (80%) and one male (20%) with mean age at inclusion of 10.6 years (4-19 years), all 5 of them presented germline *de novo* variants. All of them presented developmental delay, mainly affecting the motor and language development. Four out of five (80%) presented seizures, the remainder one (20%) only depicting EEG epileptiform activity without apparent clinical events. Of the four patients with seizures, all of them had an onset with febrile generalized tonic-clonic seizures, with a mean age of 17,75 months (8-30 months). One of them (25%) also presented atypical febrile seizures. Three patients developed focal seizures with impaired awareness and automatisms, all of them at the age of three years. At the EEG, four patients presented interictal epileptiform activity, mostly with posterior quadrant predominance (3/4). Four patients received antiseizure medication (three were treated with valproate, one of those in combination with lamotrigine, and one with levetiracetam). All of them remained long-term seizure-free or with significant improvement of the EEG abnormalities, in the case of the patient without clear clinical seizures.

Conclusion: SRRM2 variants are associated with an epilepsy phenotype mainly characterized by febrile seizures and focal seizures with impaired awareness. The response to antiseizure medications overall is excellent. Our group is recruiting a larger cohort to confirm these findings.

1251

NPRL3 new frameshift mutation in an Italian family with familial focal epilepsy with variable foci (FFEVF)

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Purpose: NPRL3 is part of a complex called GATOR1, regulating the mTORc signaling pathway: mutations in NPRL3 gene have been recently identified as responsible for about 11% of cases of focal familiar epilepsies.
Method: Here we present the case of a 34-year-old male with familiar focal epilepsy (sister, 32 years old; maternal uncle; maternal pro-cousin with drug-resistant epilepsy symptomatic of a frontal cortical dysplasia). From the age of 7 he developed stereotyped hypermotor seizures, mostly sleep-related and underwent multiple treatments with Carbamazepine, Levetiracetam, Topiramate, Zonisamide and Perampanel, defining a drug-resistant epilepsy with 2-3 seizures per month. A video-EEG monitoring demonstrated hypermotor seizures admitting a possible fronto-opercular seizure onset zone. Brain MRI and FDG-PET were negative. In 2022 we performed the Next Generation Sequencing (NGS).
Results: The NGS showed a duplication of 2 nucleotides, causing a frameshift mutation and premature stop-codon in NPRL3 gene, not found in literature:(NPRL3(NM_001077350.3):c.751_752dup (p.Ser251ArgfsTer3), Chr16_150384).
Conclusion: NPRL3 gene mutations are associated with Familial Focal Epilepsy with Variable Foci type 3 (FFEVF3), an autosomal dominant condition, with incomplete penetrance, usually related to cortical dysplasia. We discuss the role of epilepsy surgery and target therapies with mTORc pathway inhibitors.

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Recurrent focal status epilepticus due to ERBB4 exonic deletion with late onset presentation

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Purpose: Genetic syndromes associated to epilepsy have been increasingly described, especially in children. In adults, although less frequently, genomics has also gained more and more importance. A genetic basis for late-onset focal status epilepticus is rare and highly under-evaluated.
Method: A 72 years-old woman with late onset recurrent focal status epilepticus and cerebellar ataxia was studied. She was submitted to interictal and ictal EEG, continuous EEG monitoring during status, MRI and full exome examination.
Results: She developed awakening generalized tonic-clonic seizures by at age of 20 years. Seizures were initially responsive to ASMs. Focal impaired awareness seizures developed by the age of 40 years. There was a progressive seizure frequency increase and by the age of 54 years refractory recurrent focal status episodes were documented. Interictal and ictal findings during these episodes, that could last for days, consisted of fronto-central spiking. MRI showed mild cortical atrophy and moderate cerebellar atrophy. Seizures during status were characterized by loss of consciousness, bilateral arms' elevation and meaningless vocalization. Rare bilateral tonic clonic seizures were documented during status. Despite aggressive medical treatment, she persists with frequent episodes of status. She developed cerebellar ataxia by the age of 70 years, which led to falls. There was a moderate progressive cognitive deterioration. Exome sequencing revealed ERBB4 exonic deletions.
Conclusion: ERBB4 is a transmembrane tyrosine kinase of the epidermal growth factor receptor that plays an essential role in neurodevelopment. Patients and families described in the literature with this mutation presented with intellectual disability and rarely with refractory epilepsy. None had cerebellar involvement or status epilepticus. This case highlights the growing importance of genetics in the evaluation of epilepsy without clear-cut etiology. ERBB4 mutation might be related to late onset epilepsy and recurrent status epilepticus.

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Biallelic inheritance of *SCNA1* variants: clinical, genetics and functional study of an Italian family

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Purpose: Loss- (LOF) and gain-of-function (GOF) variants in *SCN1A* gene (Nav1.1 voltage-gated sodium channel), have been associated with a spectrum of neurologic and neurodevelopmental disorders (e.g. epilepsy) with different severity and drug-responsiveness (Brunklaus, Brain 2022). Most *SCN1A* variants are heterozygous changes occurring *de novo* or dominantly inherited. However, recessive inheritance has been reported in a few cases (Moretti, Eur J Ped Neurol 2021). Here, we describe 4 family members carrying two novel *SCN1A* variants, N924Y

(paternal origin) and H1382Q (maternal origin). The heterozygous parents are asymptomatic, whereas two children, who inherited both variants, present with developmental and epileptic encephalopathy. We functionally characterized the two Nav1.1 mutations H1382Q and N924Y to provide a genotype-phenotype correlation in the family.
Method: HEK293 cells were transfected with different combinations of WT and mutant cDNAs: Nav1.1 WT, H1382Q or N924Y alone, to understand the disease mechanism of single mutations; WT+H1382Q, WT+N924Y or H1382Q+N924Y to resemble the condition of mother, father and children, and compare them with WT+WT. Sodium currents have been recorded through whole-cell patch-clamp.
Results: H1382Q channels showed 50% reduced peak sodium current (LOF), while N924Y channels displayed 87% increased current (GOF) compared with WT. WT+N924Y and WT+H1382Q channels showed current levels comparable with WT+WT whereas N924Y+H1382Q channels showed 41% reduced current amplitude (LOF), suggesting that mutant subunits may interact with each other when co-expressed (Clatot et al., Nature Commun 2017). Other biophysical properties showed no difference between groups.
Conclusion: Our preliminary results show that H1382Q and N924Y variants cause subtle changes in Nav1.1 that are not sufficient to cause the disease when in the heterozygous state, as in parents. Conversely, biallelic inheritance of the two variants causes LOF in Nav1.1 that may decrease the seizure threshold and explain the disease in the children. Western blot analysis is ongoing to detect any possible interaction between N924Y and H1382Q.

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Genetic and phenotypic analysis of PRRT2 positive and negative paroxysmal kinesigenic dyskinesia

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Purpose: We aimed to expand proline-rich transmembrane protein 2 (PRRT2) variant sites and explore genotypes and phenotypes in patients with paroxysmal kinesigenic dyskinesia (PKD).
Method: We retrospectively analysed clinical data and examined PRRT2 variations by Sanger sequencing in 219 PKD patients. We compared 159 probands with and without PRRT2 mutations.
Results: Among 219 PKD patients including 99 cases from 39 families and 120 sporadic cases, twenty-one *PRRT2* variants were identified. Thirteen variants (c.879+4A>G, c.879+5G>A, c.640G>C, c.955G>T, c.412C>G, c.224C>T, c.623C>A, c.439G>C, c.884G>C, c.649C>T, c.649dupC, c.649delC and c.696_697delC) were known and 7 were novel (c.367_403delGGGTCCAGGCTGGAGTCTGCAGCCCCACCTGAACCAG, c.347_348delAA, c.835C>T, c.856G>A, c.116dupC, c.837_838insC, c.916_937del GCCCAGCGTCTGGGCCGGGTAG and c.902G>A). c.649dupC was the most common (52/74 participants (70.27%)). Eight probands with double

variants were identified. Patients with *PRRT2* variants were more likely to have a positive family history, an earlier mean onset age, and more serious PKD manifestations and complications including seizures and infantile convulsions. A higher prevalence of falling during attacks before treatment was showed yet underreported in those with *PRRT2* mutations (25.6% vs. 9.4%). The mean time to diagnosis was 7.94 years from symptom onset. Most of patients administered oxcarbazepine or carbamazepine responded well (97%).
Conclusion: We expanded the type and frequency of *PRRT2* variants and their association with complicated PKD. This study reveals that double *PRRT2* variants were more frequent than described previously. The knowledge or understanding of clinicians should be expanded to reduce time to diagnosis. Individual treatment should be administered based on patient circumstances and expectations. Novel and documented missense *PRRT2* variants pathogenicity requires further investigation.

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Yield of GATOR1 gene sequencing in a Serbian focal epilepsy cohort

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Purpose: Variants in GATOR1 genes are important etiological contributors in focal epilepsy and their strong association with drug resistant epilepsy as well as increased risk of sudden unexplained death in epilepsy warrants developing strategies to facilitate identification of patients who could potentially benefit from genetic testing and precision medicine. Our aim was to determine the yield of GATOR1 gene sequencing in a focal epilepsy cohort as well as establishing novel GATOR1 variants.
Method: Ninety-six patients with familial or nonlesional focal epilepsy with previous comprehensive diagnostic epilepsy evaluation in Neurology Clinic, University Clinical Center of Serbia, were included in the study. Sequencing was performed using a custom gene panel encompassing *DEPDC5*, *NPRL2* and *NPRL3*. Variants of interest (VOI) were classified according to criteria proposed by the American College of Medical Genetics and the Association for Molecular Pathology.
Results: We registered four previously unreported VOI in 4/96 (4.2%) patients in our cohort. Three VOI in 3/96 (3.1%) patients were classified as likely pathogenic, one frameshift variant in *DEPDC5* in a patient with nonlesional frontal lobe epilepsy, one splicogenic *DEPDC5* variant in a patient with nonlesional posterior quadrant epilepsy and one frameshift variant in *NPRL2* in a patient with temporal lobe epilepsy associated with hippocampal sclerosis. One variant in *NPRL3* in 1/96 (1.1%) patients was classified as a variant of unknown significance.
Conclusion: GATOR1 gene sequencing was diagnostic in 3.1% of our cohort and revealed three novel likely pathogenic variants, including a previously unreported association of temporal lobe epilepsy with hippocampal sclerosis with a *NPRL2* variant. Further research is essential for better understanding of the clinical scope of GATOR1 gene associated epilepsy.

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Phenotypic characterization of a *kcnb1* knock-out zebrafish model in the context of epileptic and neurodevelopmental disorders

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Purpose: Developmental and epileptic encephalopathies (DEE) refer to a heterogeneous group of devastating neurodevelopmental and epileptic disorders diagnosed during early childhood and sharing limited treatment options. *De novo* variants in *KCNB1,* encoding a voltage-dependent potassium channel, have been reported in DEE patients by displaying loss of function properties. Therefore, we need to better comprehend pathophysiological cascades involving *KCNB1* in DEE pathogenesis.
Method: We functionally characterized a transgenic deletion mutant transgenic line targeting and inactivating the zebrafish orthologue of KCNB1 (*kcnb1* gene) to explore neuronal dysregulations in this model. All experiments were performed between 0- and 6- days post-fertilization. Phenotypic, morphological analyses and electrophysiological recordings were performed during the early stages of development. In parallel, larvae were exposed to the proconvulsant pentylenetetrazol (PTZ) in order to evaluate the epileptogenic threshold of fish.
Results: The *kcnb1* knockout model does not reveal any morphological alterations in major organs compared to *kcnb1*+/- and wild-type larvae. However, an uncontrolled swimming behavior was recorded at various stages of development (coiling, evoked and spontaneous swimming). PTZ treatment induced an increased and maintained swimming distance in both *kcnb1*+/- and *kcnb1*-/- larvae characterized by fast circles and indicating a greater seizure-susceptibility. These data are in correlation with an increase of c-Fos positive neurons and by greater changes in electrophysiological recordings into the optic tectum of transgenic lines.
Conclusion: The *kcnb1* knock-out zebrafish model presents a physiological and behavioral phenotype similar to previous genetic models of epilepsy. Therefore, this novel model will be a useful tool to decipher pathological mechanisms due to *kcnb1* mutations and can pave the way of new therapeutic development for this genetic cause of rare epilepsies and related DEE disorders.

This work is supported by The Fondation de Recherche Médicale (PLP202010012460)

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Characterizing the *ATP6V0C* epilepsy phenotype: a new gene associated with genetic epilepsy with febrile seizures plus spectrum

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Purpose: Variants in *ATP6V0C* have been associated with neurodevelopmental disorders and seizures. In the present study we aim to delineate the *ATP6V0C* epilepsy phenotypes.
Method: We retrospectively analyzed 14 cases from 10 families with *ATP6V0C* variants. Cases were identified by an international network of epileptologists/geneticists. Previously published cases were also reviewed. Data was extracted for clinical history, examination, electroencephalography (EEG) and imaging.
Results: *ATP6V0C* variants were mostly missense (85%), and 57% occurred *de novo*. Average age at seizure onset was 10 months. Most common seizure type was generalized tonic-clonic (n=12), followed by absences, tonic and myoclonic. Additionally, three had focal seizures. Febrile seizures (FS) were reported in 92% of the cases. Most frequent epilepsy syndromes were genetic epilepsy with febrile seizures plus (GEFS+) and FS (n=4), whereas Dravet and Lennox-Gastaut syndrome were present in one patient each. Developmental delay and intellectual disability were described in seven cases, with the first neurodevelopmental concern identified on average at 12 months. EEG findings in eight patients showed interictal generalized or multifocal 2-5Hz spike-wave discharges, typically more prominent during sleep. Ictal recordings revealed seizures with generalized onset in 3/4 cases. Refractory epilepsy was common (n=7). Valproate was the most effective antiseizure medication, showing >50% seizure reduction in all seven patients tried, including 3 cases as monotherapy. Levetiracetam, lamotrigine, and topiramate were also beneficial. Five cases harbored variants in the transmembrane region 4 (TMR-4). These cases had a more severe phenotype with developmental delay (n=5), refractory epilepsy (n=4), abnormal neurological examination (n=3) with hypotonia and dysmorphic facial features and had evidence of delayed myelination and/or agenesis of the corpus callosum. Normal neurodevelopment was seen in all five individuals with variants involving TMR-1.
Conclusion: *ATP6V0C* variants are associated with a spectrum of epilepsy phenotypes, from FS to GEFS+, Dravet and other severe developmental and epileptic encephalopathies.

Neuroimaging

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Circular RNAs diurnal oscillation during epileptogenesis in mice

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Purpose: About 80% of people with epilepsy present circadian rhythmicity in their seizures. Circadian rhythms are the 24-hour endogenous cycles which determine the daily physiological changes and largely orchestrate gene expression. Circular RNAs (circRNAs) are a poorly explored class of non-coding RNAs highly expressed in the brain and recently were linked to epilepsy development. Although there is evidence that non-coding RNAs modulate the molecular circadian clock, the role of circRNAs are still unknown. Here, we investigated the diurnal oscillatory behaviour of circRNAs during epileptogenesis in mice.
Method: Wild type (WT) adult C57Bl6 male mice (n=5/group/time point; total n=60) underwent intra-amygdala (i.a.) kainic acid-induced status epilepticus (SE) or vehicle (PBS) injection at same time-of-day. From 24h after injections mice were transcardially perfused and ipsilateral hippocampus samples were collected at 6 different Zeitgeber Times (ZT; each 4h over 24h) for RNAsequencing and circRNA analysis. Differential expression analysis was performed using DESeq2 in R.
Results: In total 12,545 circRNAs were identified in both PBS and KA groups. The majority was classified as exonic. Interestingly, the number of significant circRNAs appears to fluctuate across the day. KA vs. PBS comparisons reveal 8-10 significant genes for 8am, 12pm and 4pm, while the tests found 0-2 significant genes for 8pm, 12 am and 4am. After multiple testing corrections (meta2d_BH.Q), only three circRNAs presented significant diurnal oscillation in the vehicle group while none in the KA, meaning that they lost their rhythms. Those are related to neuronal differentiation and blood-brain barrier integrity.
Conclusion: This pioneer study profiled circRNAs diurnal oscillatory behaviour during epileptogenesis in mice. Future studies are necessary to further understand the role of circRNAs, their rhythms and how it can impact epileptogenesis and seizure recurrence.

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Open access processing and analysis tools for personalized lesion mapping in focal epilepsy

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Purpose: The identification of a lesion in magnetic resonance imaging (MRI) significantly increases the odds of seizure freedom following resective surgery in patients with drug-resistant focal epilepsy. We describe a new open access image processing and analysis environment to identify patient-specific anomalies in brain morphology and microstructure, and showcase its utility in drug-resistant mesio-temporal lobe epilepsy (mTLE).
Method: A cohort of 31 mTLE patients (15 women; age 37.81±11.03 years) underwent high-resolution T1-weighted, quantitative T1 (qT1), diffusion-weighted, and fluid-attenuated inversion recovery (FLAIR) imaging at 3T. Multimodal MRI data were processed using the micapipe software (Rodriguez-Cruces, Royer, et al., 2022) and analysed using an automated clinical case report pipeline (https://github.com/MICA-MNI/z-brains). z-brains generates patient-specific z-score measures of cortical thickness/regional volume (CT/RV), qT1 intensity, apparent diffusion coefficient (ADC) and FLAIR intensity within cortical and subcortical grey matter against a normative database of 89 healthy controls (38 women; age 31.06±8.47 years). In addition to individual features, the pipeline also allows for the generation of multivariate deviation maps bridging available structural modalities.
Results: Feature asymmetry could correctly identify disease laterality in most patients from (i) neocortical data (percentage of patients with consistent lateralization from telemetry: CT: 64.00%; qT1: 66.67%; ADC: 67.86%; FLAIR: 45.45%; multivariate: 64.00%), (ii) regionally-sampled subcortical and hippocampal metrics (RV: 80.00%; qT1: 85.71%; ADC: 93.75%; FLAIR: 100.00%; multivariate: 92.31%), and (iii) an unfolded model of the hippocampus (CT: 67.86%; qT1: 60.00%; ADC: 81.25%; FLAIR: 75.00%; multivariate: 61.11%). Moreover, the 10% most atypical vertices within multivariate maps in nearly every patient (96.78%) overlapped, to some extent, with temporal neocortices or hippocampi (mean overlap: 42.26%±30.56%).
Conclusion: Our findings highlight the clinical utility of z-brains in the diagnosis of mTLE. Future work will integrate additional data modalities, focal epilepsy syndromes (e.g., focal cortical dysplasia, tumors), and validations. All code is openly available, fostering further development and widespread adoption.

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An algorithm to detect prolonged postictal hyperperfusion in poststroke epilepsy in light of perfusion-suppressing factors

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brovascular Medicine, Suita, Japan, [6]Kobe University Graduate School of Medicine, Neurology, Kobe, Japan, [7]Kyoto University Graduate School of Medicine, Movement Disorders and Physiology, Kyoto, Japan

Purpose: Our preceding studies developed an asymmetry method for detecting prolonged postictal hyperperfusion using a single set of postictal SPECT image in poststroke epilepsy (PSE). This study aimed to determine which factors prolong hyperperfusion and how poststroke patients can be selected for postictal perfusion imaging to diagnose PSE.
Method: This observational study enrolled 64 patients with PSE who had undergone perfusion SPECT two times of postictal and interictal scan (derivation group) and another 78 patients with PSE (validation group). We assessed factors that suppress postictal hyperperfusion by comparing the baseline characteristics, including characteristics of stroke lesions, between patients with and without the finding of postictal hyperperfusion in the asymmetry method. Furthermore, the detection rates of hyperperfusion and other clinical findings were compared between patients with and without the perfusion-suppressing factors in the derivation and validation groups.
Results: Hyperperfusion on the asymmetry method was significantly associated with absence of large stroke lesions (adjusted odds ratio, 18.88; 95% confidence interval, 1.87–190.81; P=0.013) and basal ganglia and/or thalamus (BGT) stroke lesions (adjusted odds ratio, 43.25; 95% confidence interval, 3.96–472.13; P=0.002); these two types of lesions were determined to be perfusion-suppressing factors. In the derivation group, the patients without large/BGT lesions showed a higher detection rate of postictal hyperperfusion on the asymmetry method compared to those with large/BGT lesions (90% vs. 29%, P<0.001). When limited to patients without large/BGT lesions, the detection rate of hyperperfusion (90%) in the asymmetry method was higher than the detection rates of convulsion (50%) and epileptiform EEG findings (38%) (P<0.001 for both). These statistical differences were consistent in the internal validation group.
Conclusion: The asymmetry method is useful for detecting prolonged hyperperfusion with high sensitivity for PSE patients without large/BGT lesions. We proposed an algorithm to diagnose PSE with postictal perfusion imaging through appropriate patient selection in light of perfusion-suppressing factors.

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Different cerebellar gradient alterations in temporal lobe epilepsy with and without dystonic posturing

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Purpose: Dystonic posturing (DP) is a common semiology in temporal lobe epilepsy (TLE) and has important lateralizing value for epileptogenic focus. We aimed to explore cerebellar gradient alterations in TLE patients with and without dystonic posturing.

Method: We obtained resting-state functional MRI in 60 TLE patients and 32 matched healthy controls. Patients were further divided into two groups: TLE with dystonic posturing (TLE+DP, 31 patients) and TLE without dystonic posturing (TLP-DP, 29 patients). We explored functional gradient alterations in the cerebellum based on cerebellar-cerebral connectivity and combined with independent component analysis to reveal regional cerebellar gradient changes related to cerebral motor network.
Results: There were no obvious differences in clinical features and postoperative seizure outcomes between TLE+DP and TLE-DP patients. Patients and controls all showed a clear unimodal-to-transmodal gradient transition in the cerebellum, while TLE patients demonstrated an extended principal gradient than healthy controls, more limited in TLE+DP patients. Gradient alterations were more widespread in TLE-DP patients, involving bilateral cerebellum, while gradient alterations in TLE+DP patients were limited in the cerebellum ipsilateral to the seizure focus. Moreover, TLE+DP patients expressed gradient alterations mainly in ipsilateral cerebellar regions related to cerebral motor network, more extensive in left-sided TLE group.
Conclusion: Extended cerebellar principal gradients revealed excessive functional segregation between unimodal and transmodal systems in TLE. More limited gradient extension in TLE+DP patients suggested dystonic posturing may limit the extent of gradient damage. Regional gradient changes mainly in ipsilateral cerebellum may contribute to more reliable lateralization value of dystonic posturing.

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Patient perspectives on big data and artificial intelligence in epilepsy care

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Purpose: The development of artificial intelligence (AI) technologies in epilepsy increasingly relies on large quantities of clinical data. As data can be anonymised at source, often permission is not sought from patients so there is a need to understand the perspectives of patients and their families regarding the use of their health data for these purposes.
Method: We conducted multi-level patient engagement to identify attitudes and ideas about data discovery and AI research in epilepsy. An online survey was shared through epilepsy charities including Young Epilepsy and Epilepsy Research UK. A focus group, bringing together parents of children with epilepsy, was used to gather qualitative data and in-depth insights. Information gathered from the survey and focus group was combined.
Results: Data from 55 patients and parents/carers of people with epilepsy was analysed. All respondees were comfortable with their/their child's anonymised medical data being used for epilepsy research, with 72.5% feeling that they did not need to be contacted if the study had ethical approval and the remaining 27.5% preferring to individually consent to study participation. In terms of AI technologies to diagnose epilepsy on MRI scans, 80.5% of respond-

ees were hoping this would lead to more accurate diagnoses with 78% concerned about false positives. 96% of respondees would be comfortable with AI being incorporated into their/their child's care, with 49% indicating that they would want to know details of the AI technology and how it was being used.
Conclusion: Our findings indicate that, overall, patients/carers are comfortable with their/their child's data being used for data discovery and AI research in epilepsy. Respondees are comfortable with the idea of AI technology being incorporated into their/their child's care. However, there are concerns around individual consent both for data being used for research purposes and for AI being used in epilepsy care.

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Longitudinal, in-vivo functional and molecular imaging to visualize neurodevelopment from infantile to adult age in wild-type mice

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Purpose: Tremendous efforts have been made to develop more targeted therapies for genetic developmental and epileptic encephalopathies (DEEs) with the aim to improve cognitive outcome. However, the potential effect of drugs on neurodevelopment is difficult to study and requires large prospective natural history studies in humans. There is therefore a pressing need for a sensitive and quantifiable short-term impact assessment. Small-animal functional and molecular imaging provides a way to assess neurodevelopment in a non-invasive, longitudinal, and quantifiable manner. Nevertheless, studies documenting neurodevelopmental changes in rodents at different neurodevelopmental stages (infancy, adolescence, and adulthood) are lacking.
Method: 25 wild-type mice were included. Thirteen underwent resting-state functional MRI (rs-fMRI) to assess functional connectivity (FC) and 12 underwent dynamic [^{18}F]SynVesT-1 PET imaging to visualize synaptic vesicle glycoprotein 2A (SV2A) uptake as a marker of synaptic density. All mice were imaged at three timepoints (Postnatal day (P)14-20, P35-40, and P90-100). Independent component analysis (ICA) and region of interest (ROI)-based analysis were performed for each timepoint. For PET data, kinetic modelling using an image-derived input function was performed for quantification of the radiotracer.
Results: Rs-fMRI: Infantile mice brains already display resting-state functional connectivity (FC) patterns. ICA-analysis showed the presence of the Default Mode Like Network (DMLN), known to be altered in various neurodevelopmental disorders, at the three timepoints. ROI-

based analysis revealed significantly increasing average FC in different brain regions over time.
PET: SV2A uptake was significantly higher at infantile than at juvenile age in all brain regions.
Conclusion: This study showed that small-animal rs-fMRI and [^{18}F]SynVesT-1 PET studies are feasible from P15. Similar to the human situation, we confirm that during normal rodent neurodevelopment there is an increase in FC despite a reduction in synaptic density. We propose rs-fMRI and [^{18}F]SynVesT-1 PET as valuable tools to study disease mechanisms and to evaluate treatment-response in rodent models of genetic DEEs.

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Association between capillary blood glucose levels and FDG-PET grey matter signal variation in patients with refractory epilepsy

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Purpose: 18-fluorodeoxyglucose positron emission tomography (FDG-PET) is essential for evaluation of patients with non-lesional drug-resistant epilepsy (DRE). Identification of focal hypometabolism increases a patient's odds of further surgical evaluation or resection, providing the best opportunity of attaining seizure freedom. This study aims to elucidate factors independent of a patient's epilepsy that may impact diagnostic yield of FDG-PET.
Method: We analysed a collection of FDG-PET images obtained in the routine presurgical evaluation of patients with DRE. FDG-PET images were exported and anonymized, along with patient age, body mass index, sex, radiopharmaceutical dose, uptake time, and capillary blood glucose level. Reports were reviewed to extract diagnostic results. Attenuation-corrected images were spatially normalized, and we extracted mean and standard deviation (SD) of grey matter signal intensity for each patient. Linear regression was performed using the above variables.
Results: Forty-two people with DRE were included with a median (IQR) capillary glucose at scan acquisition of 5.2 mmol/L (4.8-5.7). Radiopharmaceutical doses, uptake times, and glucose levels were within guideline recommendations. Mean and SD of grey matter intensity were both predicted by the regression models (mean: $F(6,35) = 11.9$, $p<0.001$; SD: $F(6,35) = 7.5$, $p<0.001$). Variables that significantly influenced grey matter SD included age ($\beta = -0.31$, p=0.04), sex ($\beta = 0.84$, p=0.002), and blood glucose ($\beta = -0.36$, p=0.009). High grey matter SD predicted a greater likelihood of a diagnostic scan (OR 2.17, 95% CI 0.63-7.44) although this result did not reach statistical significance.
Conclusion: In this cohort, SD of grey matter signal intensity of FDG-PET images increased with lower capillary glucose, even across a normal range. Greater signal variation may augment the visual identification of focal hypometabolism, which could improve the diagnostic yield of these scans. These data support fasting periods prior to FDG-PET acquisition and possible re-evaluation of non-diagnostic scans in the setting of high-normal glucose.

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Functional seizures (FS) show abnormal relationships between neurite morphology and inflammatory biomarkers

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Purpose: To assess links between systemic inflammation and white matter pathology in functional seizures (FS).
Method: 23 FS patients and 27 psychiatric controls (PCs) underwent multi-shell diffusion imaging and provided serum. Neurite density (NDI) and orientation dispersion (ODI) were quantified with the NODDI toolbox. Voxel-wise multiple linear regressions were conducted with the following serum biomarkers as covariates of interest: tumor necrosis factor receptor 1 (TNF-R1), TNF-related apoptosis-inducing ligand (TRAIL), interleukin (IL)-6, TNF-a, intercellular adhesion molecule (ICAM)-1, and monocyte chemoattractant protein (MCP)-1.
Results: IL-6 was positively associated with NDI in the left corona radiata and thalamic radiation in FS, and negatively in PCs. MCP-1 in the left anterior internal capsule was positively associated with NDI in FS and negatively in PCs. TNF-R1 was associated with lower NDI in FS and higher NDI in PCs within five clusters, including in the bilateral anterior corona radiata. TRAIL was positively associated with NDI in FS in the right inferior fronto-occipital fasciculus and anterior thalamic radiation, and negatively in PCs. ODI was negatively correlated with TNF-a in FS in the left posterior thalamic radiation, inferior fronto-occipital fasciculus, and inferior longitudinal fasciculus, the corpus callosum and left cingulum, and positively correlated in PCs. TNF-a was positively correlated with ODI in the right internal capsule and posterior corona radiata in FS, and negatively in PCs. ICAM-1 was positively associated with ODI in two clusters including the left anterior corona radiata, thalamic radiation, and uncinate fasciculus, and negatively in PCs. TRAIL was positively associated with ODI in the right inferior fronto-occipital fasciculus in FS, and negatively in PCs.
Conclusion: The relationship between serum inflammatory markers and white matter microarchitecture is different in FS compared to other psychiatric conditions. This study suggests the involvement of major white matter tracts in FS that have not been identified previously.

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Functional connectivity based on fluorodeoxyglucose positron emission tomography in temporal lobe epilepsy

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Purpose: The aim of this study is to investigate differences in functional connectivity between mesial vs. lateral temporal lobe epilepsy(TLE) based on fluorodeoxyglucose positron emis-

sion tomography(FDG-PET) using graph theoretical analysis. TLE groups were divided into four(left-sided lateral TLE;LLTLE, left-sided mesial TLE;LMTLE, right-sided lateral TLE;RLTLE, and right-sided mesial TLE;RMTLE) and compared with each other.
Method: We retrospectively enrolled 106 patients with TLE(15 patients with LLTLE, 14 with RLTLE, 41 with LMTLE, and 36 with RMTLE) who underwent FDG-PET scans for presurgical evaluation. Individual-level networks were constructed and measured by network parameters. We then constructed binarized group-level networks shared for more than 50% of the total subjects. Hub nodes were identified as a node with nodal degree higher than the sum of the mean and standard deviation of total node's degree.
Results: There were 52(49.1%) male and 54(50.9%) female participants. The mean age at PET scan was 29.7±10.9 years(range:9-60). The mean duration of epilepsy prior to scan was 12.7±9.0 years(range:1–34). In individual network, there was significant difference between LLTLE and LMTLE in characteristic path lengths(z=-2.3305, p=0.0198) and small-worldness values(z=2.305, p=0.0198). There was no significant difference among other groups. In group network, number of edges decreased in ipsilateral temporal regions in all groups, especially in left-sided group. Number of hub nodes was similar in all groups, but top ranked hub regions were different. These hubs were observed in contralateral areas in each group. When analyzing the identified hub regions, the pattern of connectivity was more obvious in all groups.
Conclusion: This study shows more disrupted connectivity in ipsilateral temporal regions in TLE regardless of epileptic foci. LLTLE seems to have more small-world property compared to LMTLE, however no corresponding brain regions were identified to display metabolic alterations. The functional dysconnectivity of TLE needs to be validated through additional research compared to healthy controls.

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Optimization of concurrent EEG-fMRI to improve detection of epileptogenic zone in people with drug-resistant epilepsy

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Purpose: Concurrent electroencephalogram and functional magnetic resonance imaging (EEG-fMRI) has been used to assist presurgical localization of the seizure focus in people with epilepsy with around 70% accuracy. This study aimed to improve the detection rate of seizure focus by using an optimized concurrent EEG-fMRI protocol.
Method: The optimized protocol employed a fast-fMRI sequence (sampling rate= 10 Hz) with a spare arrangement which allowed a time window of 1.9 seconds for EEG recording without radio frequency noise. Patients with a diagnosis of drug-resistant epilepsy who were candidates for undergoing surgical intervention were enrolled and received concurrent EEG-fMRI studies for mapping of fMRI BOLD signal changes related to interictal epileptiform discharges

(IEDs). The BOLD results were validated by the epileptogenic zone determined by resected brain substrate or lesion of radiofrequency thermocoagulation. All included patients followed up at our neurologic outpatient clinic for at least 1 year and ILAE surgical outcome was recorded.
Results: The EEG-related BOLD results indicated that 16 out of the 19 patients (84.2%) showed concordant finding to the epileptogenic zone determined by surgical intervention. The median number of ILAE outcomes of the concordance group was significantly less than that of the discordance group (2 vs. 5, z=-2.603, p=0.004). The good surgical outcome (ILAE 1 & 2) was significantly higher in the concordance group than that in the discordance group (n=10, 62.5% vs. n=0, 0%, p=0.047), with all patients in the discordance group having poor surgical outcomes (ILAE 3-5). Two patients showed better concordant results when incorporating the rhythmic slow waves with spikes.
Conclusion: Using the optimized protocol for concurrent EEG-fMRI to investigate the epileptogenic zone is clinically feasible. After adjusting the technical and EEG issues, the optimized protocol provides a satisfactory accuracy (84.2%) for detecting epileptogenic zone. The concordant result of BOLD signal and epileptogenic zone can predict the good surgical outcome.

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Altered cerebellar volumes and intrinsic cerebellar network in juvenile myoclonic epilepsy

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Purpose: This study aimed to investigate the alterations in cerebellar volumes and intrinsic cerebellar network in patients with juvenile myoclonic epilepsy (JME) in comparison with healthy controls.
Method: Patients newly diagnosed with JME and healthy controls were enrolled. Three-dimensional T1-weighted imaging was conducted, and no structural lesions were found on brain magnetic resonance imaging. Cerebellar volumes were obtained using the ACAPULCO program, while the intrinsic cerebellar network was evaluated by applying graph theory using the BRAPH program. The nodes were defined as individual cerebellar volumes and edges as partial correlations, controlling for the effects of age and sex. Cerebellar volumes and intrinsic cerebellar networks were compared between the two groups.
Results: Forty-five patients with JME and 45 healthy controls were enrolled. Compared with the healthy controls, the patients with JME had significantly lower volumes of the right and left cerebellar white matter (3.33 vs. 3.48%, p = 0.009; 3.35 vs. 3.49%, p = 0.009), corpus medullare (0.99 vs. 1.03%, p = 0.04), and left lobule V (0.19 vs. 0.22%, p = 0.002). The intrinsic cerebellar networks also showed significant differences between the two groups. The small-worldness index in the patients with JME was significantly lower than that in the healthy controls (0.771 vs. 0.919, p = 0.04).
Conclusion: The cerebellar volumes and intrinsic cerebellar network demonstrated alter-

ations in the patients with JME when compared with those of the healthy controls. Our study results provide evidence that the cerebellum may play a role in the pathogenesis of JME.

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Evaluation and localization of verbal memory in temporal epileptic patients using a fMRI memory mapping paradigm

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Purpose: Temporal lobe resection is a common clinical practice to alleviate seizures in drug resistant temporal lobe epileptic (TLE) patients. However, the resection of these structures can aggravate the memory deficit that TLE patients usually present. Therefore, there is an urgent need to understand the vulnerability of the mesial temporal lobe (MTL) prior to surgery. The main goal of this study is to validate a memory fMRI mapping paradigm that could help us to pre-surgically evaluate the functionality of the mesial temporal lobe in verbal memory in TLE patients.
Method: Sixteen TLE patients, 8 women with a mean age of 42 years (3,1 SE), were scanned using a verbal memory fMRI block design alternating words with non-words. During the task, patients were instructed to memorize the presented words. In addition, all patients were neuropsychologically evaluated using a Rey-Auditory verbal learning test (RAVLT) pre-surgically; mean time from neuropsychological evaluation to fMRI was 15 months (5,0 SE). The total number of learned words after five recall trials was collected as a measure of verbal learning. Then, a correlation analysis was performed between the activity during remembering words and the neuropsychological assessment in memory, at whole brain level.
Results: Our memory mapping paradigm selectively activated left MTL regions. Besides, there was a significant positive correlation between functional activity of these regions and the performance of verbal leaning in the RAVLT, showing a coupling of both measures.
Conclusion: The brain activity of the left MT area during a verbal block paradigm could help us to quantify the role of both the affected and non-affected MTL/hippocampus in the encoding of verbal stimuli in TLE patients. Localizing the function of the verbal memory and its relation with the surgical area could be a useful biomarker to better select candidates for epileptic surgery.

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Is atypical language lateralisation associated with a younger age at seizure onset? a meta-analysis

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Purpose: Atypical language lateralisation is more common in those with epilepsy than in the general population, as measured using task-based functional MRI (Berl et al. Ann Neurol. 2014;75:33-43). This is likely due to epileptogenic lesions and seizure activity in the left hemisphere disrupting language processing and triggering reorganisation to the right hemisphere. Such reorganisation is assumed to be more likely with a younger age at seizure onset, due to greater language plasticity in childhood. However, evidence for this association is mixed and can be skewed by the inclusion of individuals with early left hemisphere injuries such as strokes who are strongly right lateralised (Gaillard et al., Neurology 2007;69:1761-1771). This preregistered meta-analysis examines the consistency of this association.
Method: A literature search and screening of papers resulted in the inclusion of 31 studies. A random effects meta-analysis model with a restricted maximum likelihood estimator (Viechtbauer, JEBS 2005;30:261-293) was run in R to examine the pooled correlation between age at onset and language lateralisation across included studies.
Results: A meta-analysis of individuals with left-sided epilepsy (k=30, n=501) revealed a positive but non-significant linear correlation between a younger age at onset and more atypical language lateralisation, with a pooled effect size of 0.07 (p=.101). An I^2 value of 0% (95% CI: 0-40.8%) and a non-significant Q statistic (Q=22.85, p=.783) indicated low between-studies heterogeneity.
Conclusion: Despite long-held assumptions in the literature, this meta-analysis did not demonstrate that a younger age at seizure onset is associated with more atypical language lateralisation in individuals with left-sided focal epilepsy. Low between-studies heterogeneity suggests that there is little effect of methodological differences between studies on the pooled effect size. Given the heterogeneity of epilepsy cohorts, future studies should examine whether age at seizure onset interacts with other factors to influence language lateralisation, and whether this association is found in specific epilepsy cohorts.

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Tuberal and peri-tuberal microstructure in epileptic and non-epileptic tuberous sclerosis complex patients

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Purpose: To assess the difference in microstructure between tuberal and peri-tuberal regions in epileptic and non-epileptic Tuberous Sclerosis Complex (TSC) patients by advanced diffusion MRI.
Method: A multi-shell diffusion MRI protocol was added to the clinical brain scans of 6 TSC patients - three had epilepsy and three were seizure free. Two parametric maps were generated; neurite density index (NDI) and orientation dispersion index (ODI). A total of 98 tubers and normal-appearing corresponding regions in the contralateral hemisphere were manually

delineated on the NDI maps. If many tubers were present, the most prominent ones were chosen. Two rings surrounding the tubers/control areas, each 3 voxels in thickness, were automatically created by dilution to serve as the peri-tuberal regions. Gray matter was segmented from T1-MPRAGE images using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/) and the average gray matter values were computed for each tuber/control ROI and rings. A paired t-test was used for a comparison of average NDI and ODI values between tubers and their peri-tuberal regions. $p<0.05$ was considered statistically significant.
Results: Comparisons between tubers and their first and second rings were significant in the epileptic patients in NDI values ($p<0.005$ and $p<0.05$, respectively) and in 2 of 3 patients also in ODI values ($p<0.05$). In the non-epileptic patients only NDI showed significance between the tuber and the first ring ($p<0.0005$) and no significance was shown between the tubers and their second ring.
Conclusion: Microstructural changes in tuberal and peri-tuberal regions as characterized by advanced diffusion MRI are suggested to provide new information regarding epileptogenecity in TSC. Neurite density was found to be significantly different between tubers and peri-tuberal regions in all patients, regardless of their epileptogenic status. However, neurite orientation dispersion was found to be different only in epileptic TSC patients. MRI diffusion-based specific imaging features are suggested to aid in differing between epileptic and non-epileptic patients.

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Quantitative T2 relaxometry in temporal lobe epilepsy improves epileptogenic zone characterization: a pilot study

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Purpose: In temporal lobe epilepsy (TLE), hippocampal sclerosis (Hs) and/or temporal abnormalities may not be clearly visible on routine MRI. Quantitative MRI (qMRI) techniques, such as T2relaxometry, measure intrinsic properties of brain tissue, and thus may represent a useful addition to standardized MRI assessment, improving sensitivity in detection and lateralization of epileptogenic zone.
Method: Ten patients with TLE, (3M/7F, age:45.6±17.4) underwent 3T-MRI. The protocol comprised standard HARNESS sequences and T2relaxometry (GRAPPATINI, TR=4s, 16 echos, 0:174.4ms, spaced by 10.9 ms; Resolution: 0.45 x 0.45 x 4 mm3). For each patient, T1 images underwent standard Freesurfer pipeline, and were coregistered with the T2map. Histograms of T2 distributions were calculated in the following regions (classified as ipsi-lateral or con-

tra-lateral to EEG seizure focus): whole-brain, hippocampus, temporal lobe GM and WM. CSF voxels were masked out, to avoid high-signal contamination. Finally, for each patient and each ROI, we compared the individual histogram towards first quartile, second quartile (median) and third quartile of the cohort distribution of T2 values.
Results: Out of ten patients, 5 had clear EEG focus, 1 had bilateral electrophysiological abnormalities, 1 had conflicting diagnosis of Hs between two expert raters. Distribution of T2 values in temporal regions and in hippocampi was altered in agreement with the epileptogenic side. In particular, patients with EEG abnormalities showed the histogram peak shifted towards higher T2 values in the ipsilateral side (average contralateral peak = 55.5 ms; average ipsilateral peak = 50.6 ms). In the uncertain Hs case, all histogram parameters for the ipsilateral hippocampus were severely affected, while the contralateral side had normal values. Of note, Hs and EEG side coincided in this case (right side).
Conclusion: T2relaxometry might enhance lateralization of the epileptogenic zone. Quantification of epilepsy-related abnormalities using qMRI can improve the identification of optimal candidates for both surgical treatment and/or testing of anti-epileptic drugs.

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Prevalence and clinical significance of paroxysmal slowing in epilepsy

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Purpose: EEG is an essential tool to aid in the diagnosis and management of epilepsy. However, in nearly half of the patients, EEG is interpreted as normal. We have recently identified paroxysmal slow wave events (PSWEs), defined as EEG segments where the median power frequency falls below 6Hz for over 5 seconds, as a potential new biomarker for epilepsy. The objectives of this study were to characterize the occurrence and localization of PSWEs in patients with epilepsy compared with those without and to examine if PSWEs can serve as a biomarker for drug responsiveness.
Method: We used natural language processing (NLP) and in-house MATLAB algorithms to extract clinical and EEG data from a subset of 4686 outpatient EEGs available in the Temple University Hospital (TUH) corpus. Additionally, we manually reviewed clinician reports from a random sample of 500 TUH subjects and performed a longitudinal study on 30 and 54 pairs of EEGs from patients diagnosed as 'seizure-free' or as 'drug-resistant', respectively. All records had at least 17 common channels (10-20 system) with a recording duration of at least 10 minutes. PSWEs were characterized if detected in at least 2 channels.
Results: PSWE occurrence was significantly higher in the manually validated epilepsy (n=192) and NLP-epilepsy (n=866) groups, compared to patients without known epilepsy (n=178). Topographic heat maps showed that PSWEs were most abundant in temporal channels. The

proportion of patients with prolonged time in PSWEs was significantly higher among drug-resistant patients compared with drug-responsive patients. In recurring recordings, PSWE occurrence increased when patients became drug resistant.
Conclusion: A higher prevalence of PSWEs was observed in patients with epilepsy, with a distinct spatial pattern in bilateral anterior temporal regions. PSWEs dynamics over time may indicate disease severity and the lack of response to therapy.

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Clinical perspective, diagnosis and surgical management of type II focal cortical dysplasias, a ten-year study in our referral epilepsy center

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Purpose: Type II focal cortical dysplasias (FCD) or Taylor-type are considered to be a common cause of drug-resistant epilepsy, with some distinctive features. Often, they show successful response to a surgical approach. We aim to evaluate our series of type II FCD and define refractoriness and clinical, diagnostic and therapeutic features.
Method: An observational and retrospective analysis was carried out, regarding diagnostic results, clinical correlation with other tests (EEG/video-EEG monitoring and FDG-PET), and surgical outcomes. We included all patients with neuroimaging features consistent with type II FCD in brain MRI under epilepsy protocols, after evaluation by an experienced neuroradiologist, since 2012 to 2022.
Results: N=50 (50% women; mean age of seizure presentation: 13 years). All patients were diagnosed with focal onset epilepsy, with evolution to bilateral tonic-clonic seizures at least once in 52% of them. Drug-resistant epilepsy was present in 72% of the patients. Seizure frequency was either daily or weekly in 70% of the patients. There were 10 out of 50 cases with psychogenic non-epileptic seizures. The most frequent localization of FCD was in frontal lobe (68%), mostly in dorsolateral and premotor sulcus. 87% correlated the FCD lesion with FDG-PET hypometabolism. N=24 patients underwent surgery, and 5 others are pending. Complete seizure freedom from intervention to 2 years was achieved in 78% of those who had surgery.
Conclusion: Type II FCD are not always related to drug-resistant epilepsy. Neither do they ex-

clude the presence of psychogenic non-epileptic seizures, thus evaluating in multidisciplinary units is needed. Surgical approach offers great improvement with most of cases remaining free of seizures.

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Electrical source imaging of interictal epileptiform discharges is invariant to the vigilance state

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Purpose: Electrical source imaging (ESI) of interictal epileptic discharges (IEDs) is increasingly used in the presurgical work-up of drug-resistant epilepsy. While the vigilance state (VS) has been suggested to affect the localizing ability of IEDs in identifying the epileptogenic zone, little is known about the effect of sleep on ESI and IED characteristics.
Method: We utilized full-night high-density EEG recordings from 16 patients with focal drug-resistant epilepsy. IEDs were visually marked in each VS, and analyzed for amplitude and topography in the sensor and source spaces. ESIs were computed using the coherent maximum entropy on the mean method known to be sensitive to the spatial extent of the generator. ESIs were compared between all VSs, and with the clinical ground truth. We performed all comparisons twice, with all marked IEDs and with an equalized number of IEDs, controlling for the signal-to-noise ratio (SNR). In the source space, the effect of amplitude was further investigated with hierarchical clustering with and without considering amplitude information.
Results: Both amplitude and duration were influenced by the VS in both equalized and unequalized conditions, with the largest amplitude and duration during N3 ($p<0.001$). We did not find any effect of the VS on channel involvement ($p>0.05$). No differences were found for distance, quality, extent, or maxima distances between localizations compared to the clinical ground truth across conditions ($p>0.05$). Only when using an absolute reference (wakefulness), the sensor and source spaces were affected ($p=0.032$, $p<0.01$), with fewer channels involved and active vertices during REM. Clustering suggested the amplitude as a driver, with a more skewed distribution when the amplitude was included ($p<0.05$).
Conclusion: ESI results of IEDs are invariant to the VS, with no evidence that REM provides a better localizability. Amplitude and SNR variations rather than the VS may explain results of previous studies.

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Concordance between interictal and ictal EEG-fMRI BOLD responses in patients with malformation of cortical development

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Purpose: To investigate the concordance of blood-oxygen-level-dependent (BOLD) signal associated with ictal and interictal discharges during EEG-fMRI acquisitions in patients with malformations of cortical development (MCD) and pharmacoresistant focal epilepsy.
Method: Ten patients (8 had surgery, 24-57 years) with MCD experienced focal seizures during the EEG-fMRI exam (3T-scanner, 32-channels EEG acquisition). We performed the pre-processing and event-related analysis (MATLAB/SPM/UF²C-Toolbox) considering the times of the seizure onset and interictal spikes and relative time-shifts from -6 to +6 seconds (steps of 2-seconds). The individual unified BOLD activations were compared to the MRI and FDG-PET (available for 8 patients) abnormalities.
Results: The MCDs were focal cortical dysplasia (FCD) in 6, mild MCD (mMCD) in 3, and poly-microgyria (PMG) with heterotopia in one patient. MCD lesions were localized in the frontal lobe in 5 (50%; 2 mMCD and 3 FCD-IIb), in the temporal lobe in 2 (20%; one mMCD and one FCD-IIb), and the posterior quadrant in 3 (30%; one FCD-IIb, one FCD-IIId and one PMG) patients. Concordant localization between ictal and interictal BOLD signal occurred in 7/10 (70%) patients, including both patients with temporal lobe (100%), 2/3 (67%) with posterior quadrant, and 3/5 (60%) with frontal MCD. The most significant cluster of BOLD response and the site of the MRI lesion co-localized in 80%; the two patients with discordant MRI/BOLD response had frontal lobe FCD-IIb. The BOLD response and FDG-PET hypometabolism were co-localized in 75% of patients.
Conclusion: Our preliminary data suggest that the concordance of ictal/interictal BOLD response depends on the lesion location rather than the type of MCD. Ictal/interictal BOLD does not always overlap with the site of MCD, particularly in the frontal lobe. Integration of EEG-fMRI may add important information about the brain network dysfunction in patients with pharmacoresistant epilepsies and may be relevant for surgical outcomes.

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^{18}F-FDG-PET enhances surface-based MRI automated detection of bottom-of-sulcus dysplasia (BOSD)

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Purpose: Bottom-of-sulcus dysplasia (BOSD), is an important but diagnostically challenging subtype of focal cortical dysplasia (FCD) type II with 60% of BOSD being missed on initial MRI (Macdonald-Laurs et al. *Neurology* 2021;97(2):178-190). Surface-based MRI features are increasingly used in automated FCD detection (MELD Group, Spitzer et al.; *Brain* 2022;145(11):3859-3871). However, the combined utility of MRI and ^{18}F-FDG-PET is less established. We tested the MELD Group's machine-learning automated FCD detection method with additional ^{18}F-FDG-PET features in patients with BOSD, to see if detection rate was enhanced beyond that seen with MRI alone.
Method: 54 children and adolescents (74% operated) with MRI-positive BOSD were studied. BOSD were manually segmented on MRI. Various combinations of 12 training features (T1=8, FLAIR=2, ^{18}F-FDG-PET=2) were studied. A neural network classifier (Neural Network Toolbox, MATLAB 2020b) was trained using feature maps normalized by a group of pseudo-control subjects. Leave-one-out cross-validation assessed classifier performance. All 12 input features were used in the main analysis. Separate classifiers were trained on T1-only, FLAIR-only, ^{18}F-FDG-PET-only, and T1-plus-FLAIR features to assess discriminatory value of specific imaging modalities. For each patient, a probability map was produced and the cluster with highest probability was compared with the BOSD. Performance was the proportion of patients in whom the most probable cluster overlapped with the BOSD.
Results: When the classifier was trained using all input features, the most probable cluster overlapped with BOSD in 37/54 (69%) patients. When it was trained on ^{18}F-FDG-PET features alone, overlap was seen in 40/54 BOSD (74%). 32/54 (59%) of BOSD overlapped when using T1-plus-FLAIR, 23/54 (43%) using T1, and 12/54 (22%) using FLAIR features only.
Conclusion: Addition of ^{18}F-FDG-PET features enhances automated detection of BOSD compared to MRI-based features only. Surprisingly, ^{18}F-FDG-PET features alone performed as well as all features combined, highlighting the sensitivity of ^{18}F-FDG-PET in detecting BOSD.

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Validation of automatic 3D segmentation of extratemporal surgical lacuna using ResectVol

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Purpose: To assess the performance of the ResectVol toolbox for automatic MRI segmentation of extratemporal lacunae of extratemporal resections.
Method: We retrospectively selected 84 patients from UNICAMP and Cleveland Clinic Epilepsy Center databases. MRI data sets comprised pre- and postoperative T1-weighted MRIs of extratemporal lobe epilepsy patients submitted to resective surgery. Five individuals manually segmented the areas of resection using MRIcron. First, we updated ResectVol—already validated for temporal lobe resections [Casseb RF et al. Epilepsia Open 2021; 6(4):720-726]— to

extend its functionalities to extratemporal surgeries. Then, we calculated the Sørensen-Dice similarity coefficient (SDC), determining the spatial overlap ratio between manual and automatic segmentations. Moreover, a subset of 43 images was segmented by two different raters to estimate the inter-rater SDC. Finally, we run all processing and analyses of the images in Matlab.
Results: After processing images with ResectVol, we obtained the 3D segmented lacuna image file, a report containing the brain regions removed, and individual masks of these regions. The median SDC between manual and automatic segmentation was 0.73 (Q1-Q3: 0.55-0.81; min-max: 0.00-0.95), and the inter-rater SDC was 0.87 (Q1-Q3: 0.76-0.89; min-max: 0.00-0.97). ResectVol failed to detect the correct location of the lacuna in nine of the 84 cases, markedly those related to small lacunas and images with poor contrast between brain tissues and CSF.
Conclusion: ResectVol automatic segmentation of extratemporal lacunae is more challenging than temporal resections due to the heterogeneity of surgery locations. However, it was successful in most cases, indicating that it can aid researchers in this tedious, time-consuming task. In addition, ResecVol segments the anatomic structures within the surgical lacuna allowing for co-registration with preoperative multimodal imaging that may help in developing predictive models for surgical outcome.
Acknowledgment: Supported by FAPESP grants #2020/00019-7 and #2013/07559-3 and NIH grant NS097719.

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Seeking the invisible – volumetric analysis in non-lesional epilepsy

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Purpose: It may be challenging to determine and quantify mesial temporal sclerosis using visual assessment of images alone. The ILAE published recommendations to optimize lesion detection with MRI post-processing, including volumetry (Bernasconi, A. et al. Epilepsia 2019;60:1054-1068). We present the process of implementation of volumetry for people with epilepsy and MRI-negative scans in our tertiary referral centre for epilepsy surgery and consider data from 22 patients who underwent volumetry
Method: The temporal lobe epilepsy protocol in Beaumont Hospital met the minimum requirements set out in the HARNESS-MRI protocol. We used MRI post-processing software (Brainlab©) which conformed to the Medical Devices Regulations with functionality to calculate automatically segmented structural volumes, although it does not allow for sub-field segmentation of the hippocampus. We normalized the volumes to account for head size measurements and compiled a database of "normal" volumes derived from MRI negative scans which were reported normal. Thresholds defining a "normal" range for inter-hemispherical and population sample comparisons were established. Python automatically generated a

report and colour-coded abnormal findings.
Results: The normal database was categorised by sex and age and consists of a total of 187 anonymised patient scans. Thresholds for abnormality were identified with respect to inter-hemispherical volumes and comparison to the "normal" sample population. The format of the final report was agreed with clinicians and forms part of the diagnostic toolset. Twenty-two patients had volumetry in a 12-month period and there were abnormal volumetric findings in 50% of these. Five patients in this cohort were referred for resection, with a further 3 referred for further intra-cranial monitoring.
Conclusion: Routine volumetry for MRI-negative patients can be useful in identifying abnormalities in up to 50% of patients which may influence decisions regarding pre-surgical evaluation. There is potential for improvement through collaboration with other centres carrying out volumetry to ensure a more diverse patient demographic.

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A language task activates mesial temporal lobe

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Purpose: Mesial temporal lobe (MTL) resection risks memory deficits. Functional Magnetic Resonance Imaging (fMRI) language tasks identify language areas, but memory paradigms face methodological challenges. We studied MTL activation patterns during language fMRI.
Method: We included 18 adults and 20 children with left focal epilepsy, 27 adults and 28 child healthy controls. were typically developing. Subjects performed an Auditory Description Decision language task during 3T EPI BOLD co-registered fMRI to T1 anatomic MRI, normalized to standard space, applying hippocampus, parahippocampus, Broca's and Wernicke's regions of interest, analyzed in SPM 12.

We used a mixed model to investigate MTL activation, with activation magnitude as dependent variable, subject group (patients and controls) and age as fixed factors, side and region as repeated effects with Bonferroni correction.

To characterize language laterality index and neuropsychological (NP) score impact (LI) on MTL LI, we used ANCOVAs with Broca's and Wernicke's LI as covariates, linear regression to predict MTL LI from Broca's and Wernicke's LI, Pearson's correlations to study relationships between MTL LI and age, and NP scores as dependent variable.
Results: 95% of adults and 98% of children had individual left-lateralized MTL activation (5 or more voxels (k ³ 5), at (p £0.05) ; 66.7%) and 45 %, respectively, at the strictest threshold (p £ 0.05, FDR). There was no difference in patients versus control MTL LI. Both patient and TD children had left-lateralized MTL activation; there was no correlation between MTL LI and age; ANCOVA show significant effects of Broca's and Wernicke's LI on MTL LI. We found interactions among subject group, NP scores (varying across domains) and MTL activation, with

stronger pediatric effects.
Conclusion: We found language task MTL activation, left greater than right in children and adults, suggesting language fMRI tasks could evaluate memory function for epilepsy surgery.

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Multi-tensor diffusion abnormalities of gray matter in an animal model of cortical dysplasia

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Purpose: Focal cortical dysplasias (FCD) are characterized by abnormal cyto- and myelo- architecture and represent a frequent cause of drug-resistant epilepsy. In many cases, these lesions are subtle and go undetected with conventional imaging. Diffusion-weighted imaging (dMRI) provides a window to the microarchitecture of tissue. We investigated the ability of advanced dMRI methods to detect diffusion abnormalities in an animal model of cortical dysplasia that resembles the histology of FCD Type IIa.
Method: Adult female rats were injected with carmustine (BCNU; 20 mg/kg) (n=4) and saline solution (n=4) at embryonic day 15. Resulting pups (BCNU: n=18; Control: n=19) were scanned in vivo at P30 using a 7 T animal scanner. The dMRI images were acquired in 90 different directions, each with b values of 670, 1270, and 2010 s/mm^2, followed by fifteen b=0 s/mm^2, (spatial resolution of 0.175×0.175×1 mm^3). For dMRI analysis we included the diffusion tensor (DTI) and the multi-resolution discrete search method (MRDS) that estimates up to three tensors per voxel, which were separated into those parallel or perpendicular to the orientation of cortical columns (derived metrics are indicated with par or perp subindices, respectively). Histological validation was performed using immunofluorescence staining (MBP; 1:200 and NF200; 1:200).
Results: Single-tensor (ie, DTI) fractional anisotropy (FA) was abnormally low in motor and secondary somatosensory cortices in BCNU group. MRDS metrics revealed abnormalities of FA_{par} and MD_{perp}. , at the same cortical level. Immunofluorescence highlighted abnormalities in the myeloarchitecture in the motor cortex.
Conclusion: Our results suggest that dMRI is able to detect histological abnormalities of the cortex in early stages of development and can therefore prove useful for the identification of FCDs in clinical settings.

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Decreased surface area in epilepsy patients with postictal generalized electroencephalography suppression

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Purpose: Postictal generalized electroencephalographic suppression (PGES) is defined as the immediate generalized EEG activity suppression after seizure termination (within 30 s) with an amplitude <10 μV. It usually occurs after generalized convulsive seizure (GCS). In this study, we aim to compare the surface area of whole cortex among the epilepsy patients with PGES (PGES+), patients without PGES (PGES-), and healthy controls.
Method: Patients with at least one GCS of either generalized or focal onset recorded during video-EEG (VEEG) monitoring were enrolled. Two clinical neurophysiologists separately reviewed the VEEG and divided patients into the PGES+group and the PGES-group based on the criteria mentioned above. T1-weighted images for the patients and matched healthy controls were obtained at a 3.0 T MRI scanner. The images were processed using cortical surface-based analysis in FreeSurfer. The surface maps following the calculation of vertex-wise estimates of the surface area for each group were statistically compared based on a general linear model framework within FreeSurfer ($P<0.05$).
Results: We included 30 patients in PGES+group,21 patients in PGES-group and 30 matched healthy controls. No significant differences were noted in gender, age, age of onset, duration, seizure type, GCS frequency per year or during VEEG monitoring, EEG lateralization, application of anti-epileptic drugs and risk factors ($P>0.05$) between the PGES+group and PGES-group.Compared to healthy controls, the PGES+group showed reduced surface area in the right posterior cingulate gyrus and left postcentral gyrus, middle frontal gyrus, and middle temporal lobe; while the PGES-group presented reduced surface area in the left caudal middle frontal gyrus. More importantly, compared to PGES-group, PGES+group exhibited reduced surface area in the bilateral insula and operculum with more extensive distribution in right hemisphere. No significant surface area increase was detected.
Conclusion: PGES+group presented characteristic and widespread surface area reduction, suggesting severe seizure-related damage to the microstructure of brain and the mechanism of PGES.

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Disrupted modularity in mesial temporal lobe epilepsy using magnetoencephalography

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Purpose: Temporal Lobe Epilepsy (TLE) with hippocampal sclerosis (HS) is a network disorder with both hippocampal and distant connectivity changes. However, the changes in network modularity is not well known. We aim to characterize group level modular interactions in TLE and compare with healthy controls.
Method: Twenty-nine patients with TLE (Left:15, Right:14) who underwent MEG recording as part of their pre-surgical evaluation were considered along with 21 healthy controls. Modularity was identified by using the Louvain algorithm on adjacency matrices generated using phase lag index (PLI) for each group and intra and inter modular degree compared between the groups.
Results: Healthy controls showed 8 modules in broad band data with modules corresponding to well-known resting state networks. Both left TLE and right TLE showed fragmented modules, with a single dominant module and multiple smaller modules with ~2 nodes. Greater fragmentation was observed in the higher frequency bands. Intra modular degree was decreased in left TLE in the delta band ($p<0.01$), and the right TLE in the gamma band ($p<0.01$). Inter modular degree was decreased in left TLE in the theta and high gamma band ($p<0.01$) and in the alpha, beta, gamma and high gamma bands in the right TLE ($p<0.01$). Intra modular degree in high gamma band in left TLE was positively correlated with seizure frequency (r-0.78) and participation coefficient with epilepsy duration in the theta band(r-0.73). Right TLE modular degree showed a positive correlation with seizure frequency in the gamma band (r-0.53).
Conclusion: Our study shows a clear disruption of modular organization in both left and right TLE-HS patients presenting in different time windows corresponding to frequency channels. Modules in both groups showed increased bihemispheric, multilobar intra modular connections. A decrease in both intra and inter modular interactions in TLE was observed across multiple frequency bands suggesting a breakdown in small world architecture.

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Reconstruction of 2D MRI for subcortical shape analysis in idiopathic generalised epilepsy

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Purpose: Individuals with Idiopathic Generalised Epilepsy (IGE) have previously presented with morphometric abnormalities of the subcortical structures, suggesting pathomechanistic involvement (Whelan et al. Brain 2018; 121:391-408). 2D MRI is often acquired during the neuroradiological evaluation of IGE, whereas 3D MRI is preferable for morphometry. We compared the performance of 3D images synthesised from 2D scans against 3D scans in detecting

morphometric abnormalities in an IGE cohort.
Method: During the same scanning session, 2D and 3D MRI were acquired from 39 healthy controls and 31 individuals with IGE at the Walton Centre NHS Foundation Trust, Liverpool. 3D images were synthesised from 2D scans using DL+DiReCT and SynthSR. The scans and synthesised images were reconstructed, segmented, and parcellated. Subcortical surface shape differences between the IGE patients and the controls were evaluated. Similarities between the parcellations and shapes were measured.
Results: Dice coefficients were low across the 176 cortical parcellations but higher across the 15 subcortical structures (cortical/subcortical: 2D = .215/.361, DL+DiReCT = .198/.318, SynthSR = .217/.349). Across all regions, volumetric measures were highly correlated (volume/thickness: 2D = .990/.903, DL+DiReCT = .989/.922, SynthSR = .985/.803, $p < .001$).
In the 3D scans, surface deflations were detected in the left accumbens, right thalamus, and the caudate and putamen bilaterally of the IGE group, compared to controls (IGE/controls: males = 14/16, mean age = 32.16/32.13). The 2D scans yielded no significant shape changes, whereas the synthesised images did, some of which were not found in the 3D scans.
Conclusion: IGE patients presented subcortical shape changes suggestive of regional atrophy. Images synthesised from 2D scans led to the identification of more IGE-related subcortical shape abnormalities than the unprocessed 2D scans, alongside abnormalities not detected in the 3D scans. Synthesised images potentially facilitate morphometry with reduced MRI requirements in epilepsy, but quantitative analyses should be interpreted cautiously.

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Widespread, depth-dependent microstructural damage in the cortex of children with drug resistant focal epilepsy: a quantitative T1 and T2 mapping study

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Purpose: Widespread structural cortical abnormalities have been demonstrated in adults with focal epilepsy, remote from the putative epileptic focus, which may be due to ongoing chronic disease processes. In children with epilepsy however, focal, rather than global, cortical abnormalities might be expected, because of shorter disease-duration.
Method: We applied surface-based qT1 and qT2 to assess cortical architecture in children with drug-resistant focal epilepsy, and their relationship to clinical parameters. Additionally, we used a random forest classifier on qT1 and qT2 cortical gradient maps to assess whether

cortical microstructure patterns learnt from MRI-positive patients could classify MRI-negative patients.
Results: We report the presence of widespread, depth-mediated qT1 and qT2 increases in children with focal epilepsy. Changes were unrelated to focus area or laterality, and likely represent loss of structure, gliosis, myelin and iron changes, edema-associated free-water increases, or a combination of these. Based on the lack of associations with disease-severity measures, we suggest that such changes appear during cerebral development and represent antecedent neurobiological alterations, rather than the cumulative effect of seizure-activity or medication side-effects. A random forest classifier trained on whole-brain qT1 and qT2 surface maps from MRI-positive patients and controls could classify data from MRI-negative patients and controls not used in the training phase, suggesting the presence of a potential imaging endophenotype of focal epilepsy, detectable with or without radiologically-identified abnormalities being present. Its ability to classify young patients may suggest that such endophenotype may be present at a pre-symptomatic disease-stage.
Conclusion: These findings could have important implications for the early diagnosis of epilepsy, possibly before seizure-activity appears, with the goal of enabling timely care for patients and increasing the range and timing of therapeutic options.

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Effect of VNS therapy on MRI-assessed locus coeruleus integrity in patients with drug-resistant epilepsy

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Purpose: Vagus Nerve Stimulation (VNS) is an adjunctive treatment proposed for patients with Drug-Resistant Epilepsy (DRE) who are not eligible for surgery. However, the mechanisms of action and the neuroplasticity effects occurring in the brain following VNS administration are not fully understood. VNS mediates partially its anti-epileptic effects through activation of the Locus Coeruleus (LC), a small brainstem nucleus that constitutes the main source of norepinephrine in the brain. This study aims at assessing the effects of VNS on the LC integrity using MRI.
Method: The LC was imaged in twenty-three patients using a Magnetization Transfer-weighted Turbo-FLash (MT-TFL) Magnetic Resonance Imaging (MRI) sequence. Based on MT-TFL images, the LC mask of each patient was manually drawn by two independent raters and the intersection of the two masks was computed. For each axial slice, after centering a 5-voxel cross on the voxel with the highest intensity, the contrast was extracted in different LC subregions (25% rostral, 50% middle and 25% caudal portions) and normalized compared to a reference region located in the pontine tegmentum. A General Linear Model (GLM), was fit-

ted between the contrast of LC subregions and therapy duration, using age, sex, antiepileptic drugs, and benzodiazepine intakes as covariates. A Spearman correlation was computed between the contrast of LC subregions and therapy duration, controlling for age.
Results: Using a GLM, a significant effect was observed between therapy duration and LC contrast in the middle portion of the LC (p=0.02), while no significant effects were observed in the rostral (p=0.9) and caudal (p=0.28) portions of the LC. The middle LC contrast was positively correlated with therapy duration ($r_{Spearman}$=0.47, p=0.028).
Conclusion: Our results show that VNS therapy modulates the LC by increasing its MRI-assessed contrast. This may reflect a neuroplasticity effect occurring in the brain, potentially leading to an increased integrity of this nucleus over time.

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Does the extent of cortical malformation predict seizure activity?

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Purpose: Malformations of Cortical Development (MCD) are a heterogenous group of brain lesions, with various potential aetiologies. They can have diverse clinical presentations, including drug-resistant epilepsy. The epileptogenic potential of MCD varies widely. It is unknown from previous studies whether the extent of malformation correlates with the severity of associated epilepsy.
Method: We analysed the records of 66 patients attending Cork University Hospital due to MCD. We excluded Group 1 (abnormal cell proliferation) as these are commonly focal dysplasias and potentially curable with surgery; anti-seizure medication is the mainstay of treatment for Groups 2 & 3 (abnormal neuronal migration, and abnormal cortical organisation, respectively).
We investigated whether the extent of the MCD malformation correlated with seizure activity. We dichotomised the malformations as 'unilobar' or 'widespread' for the purposes of the study. We also investigated if any baseline characteristics were correlated with a better chance of seizure freedom.
Results: Our data have not shown a correlation between extent of malformation and seizure activity.
Conclusion: The severity of epilepsy does not correlate with the anatomical extent of MCD.

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Intact default-mode network and unimodal-transmodal integration in the isolated and connected hemispheres after hemispherotomy

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Purpose: To verify that the default-mode network (DMN) remains intact and quantify patterns of unimodal-transmodal integration in the isolated and connected hemispheres after Hemispherotomy (HT).
Method: We included 28 individuals (17 female) who underwent HT and postsurgical resting-state fMRI (age at fMRI 22.4±9.9 years [mean±SD]) and 24 healthy controls (12 female, age at MRI 31.2±12.5 years). Following fmriprep-preprocessing, DMN core nodes (posterior cingulate cortex [PCC] and anterior cingulate cortex [ACC]) were extracted in controls using canonical independent component analysis in MNI152-space. Only if sufficient tissue was preserved, isolated hemispheres were considered further. The statistical peak coordinates of the PCC and ACC in controls were used as seeds to delineate the DMN in isolated and connected hemispheres. To quantify DMN connectivity on whole-hemispheric level, the entire cortex was parcellated using an atlas by Schaefer et al. (Cereb Cortex 2018;28(9):3095-3114) resulting in 200x200 connectivity matrices. To quantify connectivity, we calculated within-network and between-network connectivity and applied a diffusion map-based gradient approach.
Results: Typical DMN connectivity patterns were found in the connected (n=28) and isolated (n=11) hemispheres after HT using ACC and PCC seeds from controls. ACC-PCC connectivity strength was significantly lower in the connected (P=0.001) and isolated (P<0.001) hemisphere than in controls but significantly >0 (P<0.001). On whole-hemispheric level, between-network connectivity in the connected (n=28) and the isolated (n=9) hemisphere was higher than in controls between the DMN and unimodal networks (visual, somato-motor, and salience networks, P<0.05). The diffusion map-based approach revealed that unimodal and transmodal networks, especially the DMN, shift along the principal gradient axis towards its center in both hemispheres.
Conclusion: Our results demonstrate that the DMN remains intact in both hemispheres after HT. On a whole-hemispheric level, unimodal-transmodal integration characterizes DMN connectivity after HT.

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Normative modelling of hippocampal morphology in epilepsy

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Purpose: New neuroimaging methods are required to improve outcomes for drug resistant epilepsy patients. We are evaluating the efficacy of normative modelling (NM) at different sample sizes and applied epilepsy population, using hippocampal segmentation and reconstruction.
Method: Hippocampal thickness was extracted from T1w Magnetic Resonance Imaging (MRI) with Hippunfold which segments and reconstructs hippocampal surfaces. Bayesian linear models were trained with the PCNtoolkit Python package on control subjects to predict normal hippocampal thickness at each vertex based on inputs of age, sex and acquisition site. Z-scores were computed to compare ground truth and predicted hippocampal thickness. Sample size was tested with a dataset of T1w 3T MRIs ($0.8mm^3$) 581 subjects (age 36-100) with a holdout set of 81 subjects for testing and sampling between 25-500 subjects for training. Applying NM in epilepsy, we used a dataset of T1w ($0.7mm^3$) 7T MRIs containing 59 subjects (27 controls, 32 epilepsy). The NM was trained and tested on 27 control subjects and applied to 32 epilepsy subjects.
Results: Distribution of thickness z-scores averaged across vertices and subjects for the 25 subject model were shifted ~0.5 standard deviations (SD) higher than larger sample size models. Mean z-scores in both the left and right hippocampus are ≥3 in the hippocampal midsections, especially along the inner fold corresponding roughly to CA2-3. In patients with known epilepsy types, a left temporal and right frontal subject had less variable z-scores. Another left temporal and bitemporal subject had z-scores ≥3 in the hippocampal midsection with the bitemporal subject having z-scores in the left tail ≤-3.
Conclusion: This analysis shows differences between smaller and larger training set size models and possibly relevant differences between epilepsy and control subjects for thickness z-scores. Larger datasets are necessary to understand the effect of larger training sets and better represent variation in hippocampal thickness.

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Distinctive brain connectivity patterns in temporal lobe epilepsy and hippocampal sclerosis: implications for cognitive function

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Purpose: Current evidence supports distinctive brain connectivity abnormalities in patients with temporal lobe epilepsy and hippocampal sclerosis (HS). This work aims to determine whether abnormalities found in HS are different in patients with structural epilepsy associated with focal cortical malformations. We compared properties of structural connectivity between two types of refractory epilepsy (HS and focal cortical dysplasia -FCD) and against a

healthy control group (HC).
Additionally, we evaluated correlations between network measures in epileptic patients with cognitive performance in verbal and non-verbal memory tests.
Method: From an MRI sample matched for sex and age constituted of 23 subjects with FCD (right FCD: n= 8), 41 with HS (left HS: n= 25) and 39 HC, brain connectivity between 80 anatomical regions was estimated. These ROIs were segmented in *FreeSurfer* v6.0, from 3 Tesla MRI using high resolution T1 images. We analyzed 2mm isotropic DWI from 32 gradients directions (Eddy currents and oposite phase FSL -TOP Up correction) , using deterministic tractography in *DSI studio* toolbox. Connectivity matrices were weighted using average fractional anisotropy. Global graph parameters were compared between groups using ANOVA, controlling the covariates of age, gender and time of disease progression. Finally, Pearson's correlation was estimated between graph measures and the Z-scores obtained from the verbal and non-verbal memory test in a subsample of HS patients (n= 33, right: n= 12). Significance was adjusted to minimize the effect of multiple comparisons (Bonferroni).
Results: We found increase in the clustering coefficient (p=.041) and transitivity (p=.037) in HS patients compared to FCD. A negative correlation was found between the clustering coefficient and delayed visual recall scores (r= -.632, p= .027) in right HS patients.
Conclusion: These findings provide insights into the distinctive brain connectivity patterns in temporal lobe epilepsy and HS and its implications in the underlying mechanisms of cognitive impairment in these conditions.

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Using brain imaging to improve individualized targeting of transcranial magnetic stimulation for generalized epilepsy

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Purpose: We report 2 general clusters functionally related to biliteral centromedian thalami (CMT) and a way to individualized applications for transcranial magnetic stimulation of generelized epilepsy.
Method: To get robust and general clusters, we analyzed the CMT-based functional connectivity pattern of healthy subjects from 3 databases: the Human Connectome Project (n=100) dataset, Center of Cognition and Brain Disorders (n=20) dataset and the TMS Center of Deqing Hospital (n=20) dataset, which varied from the manufacture of MRI scanner, field

strength and scanning parameters. Data of resting state fMRI was preprocessed in a traditional workflow. Pearson's correlation was used for CMT-based functional connectivity. General clusters corresponding to the left and right CMTs were at suprathreshold level in all groups, and located in the region of 4 cm below the scalp. For the application of individual practice, a method of watershed image segmentation was used to obtain the subject-level and general cluster-related target in space. Dice similarity coefficient (0 to 1) was calculated by measuring the ratio of overlap between intersection and sum of the volumes.
Results: The functional connectivity spatially patterns were remarkably similar on left and right CMT. Cortically, positive connectivity was detectable with the sensorimotor cortex, supplementary motor area, middle frontal cortex, medial temporal cortex, and middle cingulate (p<0.01, FDR corrected). No area of negative connectivity was found in the 3 datasets. In the MNI space, the general clusters of left and right CMT were the left sensorimotor region (cluster size= 41 voxels) and the right supramarginal gyrus (cluster size= 28 voxels), respectively.
Conclusion: This study identified the CMT spatial connectivity pattern and provide general clusters on subject-level practices that can best advance understanding and improve the individual application of transcranial magnetic stimulation technique for refractory generalized epilepsy.

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Does 7 Tesla epilepsy imaging improve diagnostic findings in daily practice?

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Purpose: The objective of this study was to implement and evaluate a 7Tesla imaging protocol with respect to both its practicality and its diagnostic value/potential surplus effect over 3T MRI in the pre-surgical work-up of patients with pharmaco-resistant focal onset epilepsies.
Method: The 7T MRI protocol consisted of T1-weighted, T2-weighted, HR-coronal T2-weighted, fluid-suppressed, fluid-and-white-matter-suppressed, and susceptibility-weighted imaging, with an overall duration of 50 minutes. Two board-certified neuroradiologists independently evaluated images and differences between 3T and 7T.
Results: Of 41 recruited patients > 12 years of age, 38 were successfully measured and analyzed. Mean detection confidence was significantly higher at 7T, with 1.95±0.84 out of 3 versus 1.64±1.19 out of 3 at 3T (p = 0.04). In 50% of the measured patients, additional findings over those at 3T MRI were observed. We further found improved delineation and detail in 88% of patients with 3T-visible lesions and the identification of a potential epileptogenic lesion in 19% of 3T MR-negative cases. Only expected, transient side-effects of the 7T protocol,

such as vertigo, were reported.
Conclusion: This 7T MRI protocol was successfully implemented for the first time at our center and proved to be both effective and well-tolerated by patients. Surplus effects over conventional 3T investigations included a more precise delineation of 3T-visible abnormalities and lesion detection in patients with previously negative 3T findings. Our diagnostic findings at 7T MRI confirm previous studies and imply potentially better surgical planning.

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Progressive myoclonus epilepsy and the cerebello-thalamic system: an MRI white matter tract study

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Purpose: Progressive Myoclonus Epilepsy (PME) is a rare generalised epilepsy syndrome, characterized by progressively worsening myoclonus, ataxia and tonic-clonic seizures. Although the heterogeneous genetic etiology of PME is well understood, how this causes such a distinctive phenotype is not. Our aim was to identify whether selective brain tracts are affected to give rise to these clinical features.
Method: Eleven individuals with PME with a confirmed genetic diagnosis and 22 controls were recruited. The MRI study included diffusion acquisition using 64 directions, b=3000s/mm^2. Fixel-based analysis was used to identify white matter pathways with significant abnormality in structural connectivity, with subsequent tract segmentation and analysis. Region-of-interest and whole brain volumetric analysis of T1 weighted images was performed. The relationships between structural connectivity measures and disease duration, and Unified Myoclonus Rating Scale were assessed.
Results: PME was associated with a diffuse pattern of white matter tract abnormality, with most severe involvement of tracts within the cerebello-thalamo-cortical network, particularly cerebello-thalamic, thalamo-cortical, cortico-thalamic, corticospinal tracts and splenium of corpus callosum. This was associated with reduced volume in cerebellum, thalamus, brainstem and mid-anterior corpus callosum. Cortico-cortical association pathways were relatively preserved. There was a significant relationship between duration of disease and mean Fiber Density-Cross section (FDC) across all significantly affected fixels (t=-2.519, p=0.03).
Conclusion: Patients with PME have extensive white matter tract abnormality. The large and dominant effect in the cerebello-thalamo-cortical networks is likely to the basis of the prominent myoclonus and ataxia. This pattern accords well with clinical, neuropathological and neurophysiological observations in PMEs, but how diverse genetic changes lead to this clinical/MR phenotype requires further elucidation.

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Amygdala pathology in temporal lobe epilepsy and correlations with diffusion MRI,

peri-ictal apnoea and SUDEP risk

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Purpose: Amygdala volume alterations have been described in temporal lobe epilepsy (TLE) patients and breathing disturbances, mostly apnoeas have been noted both ictally and postictally. Seizure severity, in particular convulsive seizures, are known to increase the risk of Sudden Unexpected Death in Epilepsy (SUDEP) and postictal central apnoea following convulsive seizures may increase this risk further. The aim of the study is to correlate the amygdala neuropathology in 13 TLE patients who underwent temporal lobectomies with the MRI diffusion metrics and postictal respiratory parameters collected pre-surgically.
Method: We acquired high-resolution T1-weighted anatomical and multi-shell diffusion images, and computed neurite orientation dispersion and density imaging (NODDI) metrics. Patients were further subdivided according to the presence of PICA, verified by VEEG. Automated immunohistochemical quantitative analysis of oligodendroglia (Olig2), myelin (SMI94), axons (Neurofilaments), dendrites (MAP2), neuron (NeuN), microglia (Iba1), astroglia (GFAP) and mTOR (pS6) were performed on the amygdala, peri-amygdala cortex (PAC), and white matter region of interest (ROI).
Results: The left amygdala volume was significantly decreased in patients compared to healthy controls ($p<0.001$). The right amygdala in the patient group again showed a decrease in volume but it was not significant. There was a negative correlation observed between MAP2 and amygdala volume. A negative correlation was also noted between Olig2 cell density and NODDI orientation dispersion index. Regarding respiratory manifestation, a significantly higher MAP2 and pS6 expression was found in patients with PICA, and the frequency of generalised seizures prior to surgery correlates with MAP2 and pS6.
Conclusion: This study reveals a link between amygdala pathology and the diffusion imaging alterations in epilepsy. Results from the current study shed light on the use of diffusion MRI in discovering histological pathologies in temporal lobe epilepsy. This enables the discovery of possible mechanisms of amygdala dysfunction, including mTOR pathway activation during seizures, that may increase risk for SUDEP.

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Functional magnetic resonance imaging for preoperative planning in pediatric epilepsy

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Purpose: A key challenge in neurosurgical treatment is to limit disease development by striving for clear margins, without causing new deficits. Mapping areas of the brain expected to play a critical role in cognitive and motor functions is a crucial goal in surgery planning and execution, and determining language lateralization and location is one of the most frequently addressed questions. Functional magnetic resonance imaging (fMRI) is considered to be robust method for establishing language lateralization and location, but the vast majority of research literature and methods used in the clinic are based on adult populations. Practical guidelines for the use of fMRI in surgical planning and our clinical experience reveal an urgent need to standardize the protocols and adapt the fMRI paradigms to pediatric patients. The purpose of the present project is to evaluate new task-based fMRI paradigms for language mapping adapted to age and mental level.
Method: An interdisciplinary group consisting of neuropsychologists, neuroradiologists and engineers at Oslo University Hospital have developed new task-based fMRI paradigms for language mapping based on validated block design paradigms for adults. Overall we have customized instructions, inter-stimulus interval and task material to make the protocols more feasible for children. Also, we have standardized protocols for preparation and practice before the fMRI examination. Participants will be pediatric patients (age 6-18) enrolled in epilepsy surgery work-up at Oslo University Hospital.
Results: To be announced.
Conclusion: Our hypotheses are: 1. Preparation and practice prior to the fMRI examination will reduce stress and anxiety and improve the conditions for the child to master the tasks in the MR scanner. 2. Adaptation of fMRI paradigms to age and mental level will increase success rates and validity of the test results, influence risk assessment and help guide surgical planning.

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Cognitive implications of amygdalar subnuclei volumes in lesional and non-lesional temporal lobe epilepsy

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Purpose: To explore the relationship between the volumes of amygdala subnuclei and cognitive performances in lesional and non-lesional temporal lobe epilepsy (TLE).
Method: 48 patients with TLE were enrolled. Nineteen patients [9 with hippocampal sclerosis (HS) and 10 with not-lesional TLE (NonL)] presented a right TLE (R-TLE) and 29 (15 HS, 14 NonL) a left TLE (L-TLE). T13D images from participants were analyzed by adopting the Free-

surfer software including the dedicated pipeline for amygdala subnuclei segmentation. Each patients underwent the same neuropsychological battery tests: the resulted raw scores were converted in Equivalent Scores and clustered in 4 majors' cognitive domains: language, verbal memory, attention/processing speed, executive functions. Linear regressions were performed to assess the relationships between the amygdala volumes and the cognitive performance in L-TLE (HS and Non-L) and in R-TLE (HS and Non-L).
Results: Linear regression analyses demonstrated a positive relation between verbal memory performances and the volume of the bilateral cortical nucleus in L-TLE-HS patients (Ipsi: β=.681, p=.005; Contra: β=.661, p=.007). In L-TLE-NonL, a bilateral whole amygdala enlargement is associated to lower scores in language (Ipsi: β=-.650, p=.012; Contra: β=-.545, p=.044) and executive function performances (Ipsi: β=-.649, p=.012; Contra: β=-.566, p=.039). In R-TLE-NonL the bilateral increase of volume in the cortical nuclei was related to better performances in attention and processing speed (Ipsi: β=.665, p=.036; Contra: β=.719, p=.019), while an increase of the volume of the ipsilateral medial nucleus was associated to verbal memory decline (β=-.675, p=.032). No significant relationships were observed in R-TLE-HS patients.
Conclusion: Our results suggest an impact of the amygdala subnuclei volumes on the cognitive profile of patients with TLE, with variability in HS and NonL patients. Intriguingly, an increase of amygdala volumes appears having a protecting cognitive effect in R-TLE, whereas the opposite is observed in L-TLE.

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Machine learning shows pattern differences during face and word encoding in temporal lobe epilepsy

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Purpose: Memory encoding involves frontal, mesial, and lateral temporal lobes. Temporal lobe epilepsy causes memory dysfunction. In Hippocampal Sclerosis (HS), functional MRI reveals memory network impairments beyond the affected hippocampus. Machine learning (multivariate pattern analysis, MVPA-fMRI) analyses patterns of activity across voxels in brain regions associated with individual memory traces, unlike standard fMRI investigations. MVPA-fMRI was used to evaluate pattern differences during face and word encoding in TLE due to HS to healthy controls in medial and lateral temporal Regions of Interest (ROIs) bilaterally.
Method: 22 healthy controls and 41 patients with HS (18 left) performed a word and face memory encoding vs rest task. Mesial (hippocampus, parahippocampal and fusiform gyri) and lateral temporal (superior, middle, and inferior temporal gyri) ROIs were delineated, and pat-

tern classifiers were trained to learn the patterns of activity related to encoding faces, words, and rest across voxels within these ROIs. Leaving out one subject per class cross-validation was used to investigate discernible representations within each ROI in patients compared to controls. Chi-square after Bonferroni correction was used to compare ROI classification accuracies ($p<0.05$).
Results: In both RHS and LHS, the classifier was unable to classify patterns related to faces in the right lateral temporal ROIs compared to controls where there were discernible face representations within these ROIs.
In RHS, the classifier was unable to accurately classify word representations within the left lateral temporal ROIs compared to controls.
Conclusion: While conventional fMRI has indicated decreased activations in the diseased hippocampi relative to healthy controls, MVPA-fMRI identified regions beyond the hippocampus with indistinctive patterns of the face and word encoding compared to controls. These findings suggest that MVPA-fMRI research in TLE may be valuable for analyzing patient-specific memory representations rather than merely "activations." This may help tailor surgery to reduce memory deterioration.

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Estimated disease progression trajectory of white matter disruption in focal epilepsy: a data-driven machine-learning approach

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Purpose: While progressive brain alterations in focal epilepsy have been suggested recently, each patient's trajectories and associated factors are not known. This study aimed to identify disease progression pattern of white matter damages as well as its association with clinical parameters.
Method: We analyzed diffusion tensor imaging (DTI) of 212 patients with focal epilepsy and 270 age/gender matched healthy controls from the same scanner and protocol and calculated mean fractional anisotropy (FA) values within 20 white matter tracts from JHU atlas. Subtype and Stage Inference (SuStaIn) algorithm was used to identify progression trajectory of FA changes, which was analyzed to assess its relationship with clinical parameters, including age of onset, duration of disease, focal-to-bilateral tonic-clonic seizures, seizure freedom, and number of anti-seizure medications (ASMs). Brain-age scores derived from structural T1-weighted MRI (predicted brain-age minus chronological age) were also calculated.
Results: SuStaIn identified 60 stages of white matter damage progression, in which the forceps and superior longitudinal fasciculus (SLF) are initially affected, and then damages within anterior thalamic radiations (ATR), cingulum, inferior fronto-occipital fasciculus (IFOF) and uncinate fasciculus (UF) follow. More progressed stages were associated with disease duration ($R=0.317$, $p<0.001$) and number of ASMs ($R=0.292$, $p<0.001$). Stage progression was

also associated with brain-age score from structural MRI (R=0.311. p<0.001). In patients with temporal lobe epilepsy (TLE), hippocampal sclerosis and existence of interictal psychosis were also associated with progression (p<0.001).
Conclusion: We observed specific patterns of progressive white matter damage in focal epilepsy. Disease progression was associated with duration of epilepsy and number of ASMs. Stage progression also well reflected abnormal aging of brain.

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Double cortex syndrome: a case report

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Purpose: Double cortex syndrome is a rare familial syndrome with X-linked dominant inheritance and most frequently presents with developmental delay and seizures.
Method: We present 25 years old female presented with seizures and had double cortex syndrome on MRI
Results: 25 years old female presented with the complain of staring spells and fainting episodes. Her attacks began at the age of 5. Valproic acid treatment was initiated. She left the school at the second class due to low academic performance. Seizure semiology composed of staring which occurs several times a day and some of the were accompanied by tonic spasms in the hands. During these episodes, she was unresponsive. Her birth history was normal. No similar illness was seen in the family. Neurological examination was normal. Detailed neuropsychological evaluation revealed that there was a moderate impairment of attention. Long term video EEG showed atypical absence seizures accompanied with 2-2.5Hz spike and wave complexes. After initiation of levetiracetam and lacosamide seizure frequency dropped to once a week. Magnetic resonance imaging shown a heterotopic band of grey matter interposed among cerebral white matter and cortex with a thin frame of intervening white matter. She was discharged and prescribed antiseizure medications and was informed regular outpatient follow-up.
Conclusion: Double cortex syndrome is an infrequent and severe syndrome which needs to be diagnosed by using advanced imaging modalities like MRI. Counselling of the family about prognosis and genetic counseling is essential.

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BOLD fMRI functional connectivity informed by interictal epileptiform discharges in high-risk and low-risk SUDEP epilepsy patients

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Purpose: According to recent literature, interictal epileptiform activity (IEA) might provide a facilitating environment for Sudden Unexpected Death in Epilepsy (SUDEP) to happen. Here, we explore the effects of IEA on the functional connectivity between regions of interest (ROIs) known to be involved in the SUDEP pathogenesis and the rest of the brain in a population of high risk (HR) and low risk (LR) SUDEP epilepsy patients.
Method: From the entire database of epilepsy patients investigated with EEG-coregistered to fMRI (EEG-fMRI), 39 were selected based on the following criteria: 1) IEA during EEG-fMRI; 2) age > 16 years. Patients were stratified in HR and LR according to SUDEP-3 and SUDEP-7 inventories. Additional stratification was performed based on the occurrence of tonic-clonic seizures (GTC-criteria) the year before the EEG-fMRI. Seven ROIs were considered: Anterior Cingulate Cortex, Insula, Brainstem, Thalamus, Amygdala, Putamen. The IED-related functional connectivity between the ROIs and the rest of the brain was investigated through a Psycho-physiological Interaction (PPI) analysis.
Results: SUDEP-7 revealed 15 HR and 24 LR patients, SUDEP-3 28 HR and 11 LR, GTC-criteria 19 HR and 13 LR. In the SUDEP-7 and GTC stratified groups, PPI analyses show in HR versus LR an increased IEA-informed functional connectivity between amygdala, thalamus and putamen seeds and supramarginal gyrus (SMG) and a decrease functional connectivity between the same ROIs and motor and premotor cortex. These patterns are consistent with the PPI results obtained with the same approach in one patient out of our database classified as “Probable SUDEP”.
Conclusion: Our findings suggest that in SUDEP and HR patients compared to LR, IEA modulate the functional connectivity between specific subcortical ROIs and brain networks involved in response to stimuli and surroundings (SMG) and in the regulation of the cardiovascular system (premotor cortex) thus providing new insights in the pathogenesis of SUDEP.

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A novel geometry-based analysis of hippocampal morphometry in mesial temporal lobe epilepsy

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Purpose: We introduce a novel geometry-based tool that allows point-wise morphometric analysis based on an intrinsic coordinate system of the hippocampus, apply it to mesial temporal lobe epilepsy (mTLE), and compare it to conventional volumetric analysis.
Method: We included 204 individuals with mTLE (109 female, age at MRI 30.0±13.5 years [mean±SD], hippocampal sclerosis [HS-mTLE] subtype 1/2/3: n=129/14/3, MRI-negative TLE: n=58) and 57 healthy controls (34 female, age at MRI 36.4±10.6 years). FreeSurfer-derived segmentations of hippocampal subfields based on T1-weighted 3T-MRI were subjected to

a geometry-based analysis using the first eigenfunction of the anisotropic Laplace-Beltrami operator to delineate hippocampal boundaries, and solutions of Poisson's equation for each pair of boundaries to define an internal coordinate system of the hippocampal mid-surface. This coordinate system was used for point-wise measurements of hippocampal thickness and other features such as curvature and FLAIR signal intensity.
Results: Using point-wise analysis, we found significantly lower thickness and higher FLAIR signal intensity in the entire affected hippocampus of individuals with HS-mTLE as compared to controls. In the contralateral hippocampus of HS-mTLE and the affected hippocampus of MRI-negative mTLE, we observed significantly lower thickness in the presubiculum than in controls. Impaired verbal memory was associated with lower thickness in the left presubiculum in HS-mTLE (all $P<0.05$, threshold-free cluster-enhancement). These findings could not be observed using conventional volumetry (Bonferroni-corrected $P<0.05$). When comparing different HS-mTLE histological subtypes, we observed higher curvature in subtype 3 than in subtypes 1 and 2 in the cornu ammonis 1 region ($P<0.05$). However, these groups did not differ regarding hippocampal thickness or FLAIR signal intensity.
Conclusion: We show that point-wise measures of hippocampal morphometry can uncover structural alterations not measurable by volumetry while also reflecting histological underpinnings and verbal memory.

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Blood-brain barrier dysfunction in piriform cortex, amygdala and hippocampus in temporal lobe epilepsy using quantitative MRI

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Purpose: To investigate the integrity of the blood-brain barrier (BBB) of the piriform cortex, amygdala, and hippocampus in temporal lobe epilepsy using quantitative MRI.
Method: We included 29 individuals with drug-resistant focal epilepsy (age at MRI 29.2±7.4 years [mean±SD], 12 temporal lobe epilepsy [TLE], 19 extratemporal lobe epilepsy [ETLE]). In all subjects, quantitative T1 images (qT1) were acquired after gadolinium was injected ictally and interictally. Additionally, a native qT1 image (without gadolinium) was acquired. The ictal and interictal images were co-registered to the native qT1 image, and difference maps were calculated (ΔqT1pi=interictal-postictal, ΔqT1ii=native-interictal). We manually labeled the piriform cortex and segmented the whole cortex, hippocampus, and amygdala using FreeSurfer. Verbal and figural memory scores were retrieved from clinical records.
Results: In TLE (n=12), ΔqT1ii in the piriform cortex was significantly higher than in the whole-cortex mask ($P=0.03$), while there was no significant difference between the amygdala or hippocampus and the whole-cortex mask ($P>0.17$). In ETLE (n=19), ΔqT1ii was not significantly different between temporal structures and the whole-cortex mask ($P>0.05$). ΔqT1pi

did not differ from the whole-cortex mask and temporal structures in TLE and ETLE (P>0.8). In a linear regression model across TLE and ETLE (n=29), we found a significantly stronger increase in ΔqT1ii with disease duration in the piriform cortex than in the whole-cortex mask (P=0.029), while the increase in hippocampus and amygdala were not significantly different from the whole-cortex mask. Regarding temporal cognitive deficits, ΔqT1ii in the piriform cortex, but not the hippocampus, amygdala, or whole-cortex mask, was significantly associated with stronger verbal memory deficits (P=0.04).
Conclusion: Our results show that a BBB dysfunction occurs interictally rather than ictally in the piriform cortex in TLE and is associated with disease duration and temporal cognitive deficits. This highlights the central role of the piriform cortex in TLE.

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Topological discrimination network in people with epilepsy: the comparison of the topological discrimination network and the default mode network

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Purpose: To compare the topological discrimination network (TDN) with the default mode network (DMN) in people with TLE and health controls
Method: People with TLE and healthy controls were enrolled.The imaging data of structural MRI, task and resting-state functional MRI (fMRI) data were obtained at a 3T scanner.After the resting-state scan, the task-fMRI data was acquired while participants performed the topological discrimination task (finding a “O” from the rest of three “S” shapes) and the local discrimination task (finding a mirror “S” from “S” shapes) in the scanner. A group level analysis was conducted to reveal the TDN, which was defined by the contrast between topological and local discrimination task ($p < .001$). The dynamic change of BOLD response to each task was calculated to descript the difference between the TDN and the DMN.
Results: In 21 patients, the average age was 26.1 years and the average correct rate of topological discrimination task was 96.6%, which had no significant difference from the control group. Compared to the local discrimination task, the topological discrimination task elicited deactivation of specific regions which were consistent with DMN (posterior cingulate cortex, lateral parietal lobe, medial prefrontal cortex, anterior lateral temporal lobe, and medial temporal lobes) in two groups. Furthermore, DMN deactivation (resting state vs local discrimination) in the patient group was normal and did not differ significantly from control group, whereas TDN deactivation was significantly different from control group in 20 patients (95.2%).
Conclusion: The current data showed that TDN and DMN shared similar deactivation areas.

TDN were impaired in patients with TLE and it may even have higher sensitivity than DMN in them. To confirmed the sensitivity and specificity of TDN in TLE, the positive/negative control was enrolled.

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The executive profile of persons with temporal lobe epilepsy with hippocampal sclerosis and juvenile myoclonic epilepsy

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Purpose: Temporal Lobe Epilepsy with hippocampal sclerosis (TLE-HS) and Juvenile Myoclonic Epilepsy (JME) have evidence of executive function (EF) impairments. Therefore, this study aimed to (1)compare the EF between persons with TLE-HS, JME, and controls and (2)identify particular EF deficits in these types of epilepsy.
Method: We evaluated 85 consecutive persons with TLE-HS (60% female; mean 40 years [SD 11.7]; mean IQ 86.7 [SD 12.3]), 102 persons with JME (57.8% female; mean 27 years [SD8.5]; mean IQ 97.5 [SD 12.7]), and 63 controls (59.4% female; mean 30.3 years [SD10.2]; mean IQ 92.3 [SD10.6]) with a comprehensive neuropsychological assessment for EF. We used ANOVA and chi-square to compare demographic aspects and ANCOVA to compare EF (sex, age, and IQ as covariates) with Sidak posthoc.
Results: TLE-HS and JME had worse performance in Stroop time ($p=0.006$;$p<0.001$) and errors ($p=0.007$;$p<0.001$), Trail Making Test (TMT) A time ($p<0.001$;$p<0.001$), TMT B errors ($p<0.001$;$p=0.016$) and Wisconsin Card Sorting Test (WCST) perseverative errors ($p=0.026$;$p=0.003$). TLE-HS had worse performance in Conners' Performance Test (CPT) omission errors ($p=0.004$) and reaction time ($p<0.001$). JME performed worse than controls in WSCT perseverative responses ($p=0.014$). TLE-HS performed worse than controls and JME in TMT B time ($p<0.001$;$p=0.016$). JME had worse performance than controls and TLE-HS in WCST failure to maintain the set ($p<0.001$;$p<0.001$), CPT commission and omission errors ($p<0.001$;$p<0.001$), reaction time ($p<0.001$;$p<0.001$), and variability ($p<0.001$;$p<0.001$).
Conclusion: TLE-HS and JME present distinct executive profiles. JME had worse performance in working memory, impulsivity, selective attention, pattern response consistency, and vigilance than TLE-HS. TLE-HS and JME performed worse in alternated attention and inhibitory control tests than controls. However, TLE-HS had slower mental processing compared to those with JME. Distinct epileptic syndromes may demand different neuropsychological approaches in assessment and rehabilitation.

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Theory of mind evaluation in generalized epilepsy patients: proposed model

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Purpose: Many neuropsychiatric, neurodevelopmental, and neurodegenerative disorders produce Theory of Mind (ToM) impairment. Recent guidelines recommend social cognition evaluation, including ToM for neurological diseases as a routine exam, such as in frontotemporal dementia. There is no specific recommendation for epilepsy patients besides numerous studies pointing out ToM impairment in this population, including meta-analysis. We evaluated a model for ToM testing in epilepsy patients as part of a routine neuropsychological evaluation, its feasibility, and comprehension in a tertiary center.
Method: A transversal study in a referenced Epilepsy Outpatient Clinic evaluated patients with idiopathic generalized epilepsies including juvenile myoclonic epilepsy. Theory of Mind (ToM) was assessed through the faux pas recognition test - short version and reading the mind in the eyes test. Psychological symptoms were measured by inventories (Generalized Anxiety Disorder 7 and Neurological Disorders Depression Inventory for Epilepsy) and also a neuropsychological profile of executive function (Stroop test, Wisconsin, Fluency, Digit Span) and intelligence (Wechsler Abbreviated Scale of Intelligence) as a complimentary evaluation of possible confounders. Tests were timed as part of the feasibility evaluation. A Likert three-point scale of difficulty was applied for the ToM tests.
Results: All patients were young <40 years old, mainly female (>80%), with a good educational level (>8 years of schooling). Intelligence was within average. ToM tests lasted <50 minutes (>80%). All patients reported an excellent comprehension of the test, which was considered moderate to hard in terms of difficulty (>80%).
Conclusion: The evaluation of ToM in epilepsy patients is a viable model in a tertiary center due to its length. It is inappropriate for primary and secondary care and should still be restricted for study protocols in epilepsy patients. Further studies in ToM in Epilepsy patients should be performed to better comprehend its clinical implications in this population.

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Attachment style and emotional regulation of patients diagnosed with psychogenic non-epileptic seizures

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Purpose: Early relationships with primary caregivers are considered as key factors in the etiopathogenesis of many mental disorders and they are affecting emotional regulation. Study

focused on the attachment style and emotional regulation in adult patients with psychogenic non-epileptic seizures (PNES).
Method: The presence of maladaptive emotional regulation in large sample of patients with PNES was measured by the Czech research version of the ASQ and DERS, and the type of attachment style by PBI and ECR.
Results: Significant differences in the caregiver style - father and mother overprotection (PBI) was increased in the PNES patients. The most frequent type of attachment in PNES was type 2 (preoccupied). Patients with PNES had greater emotion dysregulation in DERS.
Conclusion: This study confirmed certain attachment types in patients with PNES. The identification of specific patterns in attachment and their connections to emotional regulation may be important for further use in reaching a differential diagnosis and administering tailored psychotherapy of patients with PNES.

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Twelve-month analysis of BUTTERFLY: an observational study to investigate cognition and other non-seizure comorbidities in children and adolescents with Dravet Syndrome (DS)

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Purpose: DS is a severe and progressive genetic DEE that typically begins in the first year of life. It is characterized by high seizure frequency (SF) and severity, intellectual disability, and ataxia/motor abnormalities. There remains a need for therapies to reduce SF and improve non-seizure comorbidities. There is a lack of prospective long-term data regarding the progression of substantial non-seizure comorbidities. This fully enrolled study evaluates neurodevelopment, adaptive function, gait performance, executive function, as well as SF in patients with DS over 24 months (m).
Method: BUTTERFLY is an ongoing, multicenter, longitudinal study in the US of 36 patients aged 2-18 yrs with genetically confirmed DS whose seizures are not controlled by their current antiepileptic drugs. Data cutoff was 07Mar22, after patients completed their 12m visit.
Results: Patients (n=36) enrolled equally across age groups: 2-7, 8-12, and 13-18 yrs; 61% were female, 94% were white, and 14% were Latino. Across all patients, mean age of seizure onset was 5.1m (range 2-12m). SF was variable with no clear trends. Three patients were free of convulsive seizures during the 4-week baseline and/or 12m follow-up. Bayley-III developmental quotient and Vineland-III composite showed no significant change over 12m though small improvements were observed in receptive communication scores. Most patients performed in the dynamic range of Gillette Functional Assessment Questionnaire at baseline

with little change in mean total scores over 12m. Many patients performed on the higher end of the Behavior Rating Inventory of Executive Function – Preschool global executive composite scale suggesting difficulties with executive function with little change observed.
Conclusion: Data suggest these outcomes remain relatively stable over 12m in patients with DS. Data suggest these scales may be useful for DS clinical studies. BUTTERFLY will provide valuable insights on seizure and non-seizure manifestations in patients with DS.

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Differences of neuropsychological profiles between temporal lobe epilepsy with hippocampal sclerosis and without hippocampal sclerosis and associated clinical factors

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Purpose: This study was aimed to broaden understanding of neurocognitive profiles in temporal lobe epilepsy with or without hippocampal sclerosis (TLE-HS or TLE-noHS). We were also interested in associated clinical factors which contributed to differences of the cognitive scores between groups.
Method: Eligible consecutive patients between 2014 to 2021 who underwent neuropsychological tests (NPTs) in Chulalongkorn Comprehensive Epilepsy Center were recruited. We defined as having TLE with or without HS by magnetic resonance imaging findings. The NPTs included Wisconsin Card Sorting Test, Stroop Color-Word Test, Trail Making Test, Wechsler Adult Intelligence Scale - fourth edition and Wechsler Memory Scale - fourth edition.
Results: Among 109 recruited patients, TLE-HS (n=81) were younger at onset of epilepsy, longer duration of epilepsy, higher number of patients who had history of febrile seizure (FS), higher number of carbamazepine (CBZ) user, and lower number of patients with seizure freedom, as compared with TLE-noHS (n=28). NPT results showed that verbal comprehension index (VCI), auditory memory index (AMI), delayed logical memory (LM II) and delayed verbal paired association (VPA II) were significantly lower in TLE-HS. Upon univariate analysis, lower VCI score in TLE-HS was associated with early-age onset of epilepsy, long duration of epilepsy, presence of generalize tonic-clonic seizure, history of FS and some antiseizure medication use i.e., CBZ, topiramate and phenobarbital. Whereas a lower score of AMI, LM II, and VPA II in TLE-HS were associated with history of status epilepticus. However, upon multivariate analysis after adjustment with significant associated clinical factors, only VCI was an independent predictor for differentiating TLE-HS from TLE-noHS.
Conclusion: Our findings suggest that TLE-HS had unique clinical characteristics and neurocognitive profiles different from TLE-noHS. In clinical practice, we should bear in mind that NPT scores might be affected by some clinical factors and only VCI is a reliable test to help differentiate these two conditions.

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Are reaction times more sensitive to antiseizure medication than visuomotor speed and executive functions?

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Purpose: To evaluate the sensitivity of the computerized assessment of reaction times to antiseizure medication (ASM) in comparison to paper-pencil measures of visuomotor speed and executive functions.
Method: In this cross-sectional study in 519 patients with epilepsy we assessed alertness via the computerized measurement of simple reaction times (SRT; subtest of the NeuroCog FX®) and executive functions via the EpiTrack® including a subtest on visuomotor speed (Trail-Making-Test A; TMT-A). Analyses focused on the concordance of impairments concluded by the different measures and the relation of the standardized test results to parameters of the pharmacological treatment of epilepsy, i.e. number of concomitant drugs and the cumulative defined daily dose (DDD) as well as the presence/absence of specific ASM.
Results: The EpiTrack® indicated executive deficits in 54.1% of the patients. Impairments in alertness and visuomotor speed were observed in 45.9% versus 38.9% of the patients with a concordance of 64% and an intercorrelation of r=.35 ($p<0.001$). Significant inverse correlations with the number of ASM were found for all three cognitive parameters (EpiTrack®: r=-.33; TMT-A: r=-.26; SRT: r=-.16, p´s<0.001). The correlations regarding the cumulative DDD were slightly lower (EpiTrack®: r=-.27; TMT-A: r=-.18; SRT: r=-.15, p´s<0.001). In addition to the number of ASM, stepwise regression analyses also identified associations between individual ASM and executive function (negative: valproic acid, phenobarbital; positive: brivaracetam) and visuomotor speed (negative: phenytoin, valproic acid, zonisamide, and perampanel). Alertness was not related to specific ASM.
Conclusion: The assessment of executive functions and visuomotor speed appears more sensitive to the pharmacological treatment of epilepsy than the measurement of reaction times. These findings may help in the selection of valid measures for the monitoring of cognitive side effects.

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Can epilepsy patients in india benefit from tele-administration of neuropsychological rehabilitation? a single arm pilot feasibility study

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Purpose: The advent of COVID-19 gave the opportunity to examine the feasibility and efficacy of tele-administration of a paper-pencil Neuropsychological Rehabilitation (NR) program standardized for adult patients with Drug Refractory Epilepsy (DRE).
Method: 10 patients were recruited in a single arm pilot feasibility study. They were aged 18-45 years, had a diagnosis of DRE in the last 1.5 years, had undergone epilepsy surgery atleast 3 months ago (if surgical), had fluency in Hindi or English with at least primary level of education, IQ > 80 and the availability of a caregiver. NR manuals were couriered to six patients while four volunteered to get them printed. NR entailed psychoeducation sessions on the neuropsychological aspects of epilepsy including compensatory training for upto 4 hours. These were followed by 6 weeks of retraining activities for attention, verbal memory and visual memory including weekly telephonic sessions.
Feasibility was determined using 1) agreement to participate 2) attrition, and 3) adherence. Word Lists, Digit Span, Everyday Memory Questionnaire-13 and Quality of Life in Epilepsy-31 were used in pre and post tele-assessment through HIPPA complaint platforms on laptops/smartphones. Group analysis was computed using paired t test. In the absence of data available to calculate reliable change indices for objective measures, clinically meaningful change was calculated using standard deviation method.
Results: The NR was found to be feasible. On group analysis, significant improvement was noted in learning ($p < 0.001$), delayed recall ($p < 0.001$), long-term retention ($p < 0.001$), patient and caregiver reported everyday memory failures ($p < 0.001$) and total quality of life ($p < 0.001$). On individual analysis, 60% showed meaningful improvement on learning and delayed recall. 50% improved on long term retention, 30% on recognition and 70% on quality of life.
Conclusion: Use of tele-neuropsychology for NR is promising in low resource settings and ensures wider outreach of this specialized service.

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Is it epilepsy, Or Is It "X"? Turner Syndrome as a confound in epilepsy evaluation and care

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Purpose: Turner Syndrome (TS) is a genetic condition affecting only those with assigned female gender at birth. Its hallmark diagnostic finding is a partial or complete deletion of one X chromosome. In addition to a clear and prominent physical phenotype, this syndrome is also characterized by a far-less-documented cognitive profile. The purpose of this case study is to explore the cognitive symptomology in an individual with Turner Syndrome as a confounding variable for epileptogenic zone localization and functional testing due to suspected epileptogenic zone being ipsilateral to areas of deficit typically seen in those diagnosed with Turner Syndrome.

Method: This case study scrutinizes the medical history and epilepsy workup of an individual diagnosed with Turner Syndrome. It then examines the neurocognitive profile gleaned during comprehensive neurocognitive evaluation, as part of a workup for epilepsy care.
Results: The resulting neurocognitive profile highlighted stark and prominent weaknesses in nonverbal/visual processing skill (SD=-1.60), spatial/perceptual reasoning (SD=-1.60), visual memory (SD=-2.5), visual-motor integration (SD=-4.40), and cognitive shift (SD=-1.20). These findings are noteworthy, especially when juxtaposed to an otherwise WNL performance on verbal measures (e.g., verbal LDFR SD=1.5) and otherwise intact cognitive skill and functioning.
Conclusion: Turner Syndrome is the most frequent sex abnormality in individuals with assigned female gender. While heretofore still considered an infrequent comorbid diagnosis, some literature has found associations between TS and epilepsy. It is of critical importance to thoroughly evaluate and describe the cognitive profile of individuals with TS given its expected pattern of domain-specific attenuation, as prominent localizing weaknesses may otherwise be considered representative of an epileptogenic zone. Clear functional neurocognitive findings should also be coupled with structural and functional neuroimaging, in addition to electrographic mapping (i.e., EEG) as a best-practice standard in order to maximize epilepsy care planning for patients, which should also assist in managing unexpected cognitive and functional post-surgical outcomes.

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A web app based screening tool for social cognition in people with epilepsies

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Purpose: The ability correctly to understand social signals depends on the integrity of networks that are often affected in people with epilepsies (PWE), particularly Temporal Lobe Epilepsy (Steiger et al. Epilepsy Res. 2017;134:33-40.). Impacted PWE may experience a lower quality of life and struggle with maintaining jobs and relationships. In spite of this knowledge, testing for social cognition in clinical settings is lacking or insufficient (Eicher et al. Acta Epileptologica 2022;4-24). We are attempting to make screening for social cognition more accessible by developing a short test of complex emotion recognition.
Method: COSIMO (Cognition of Social Interaction in Movies, https://cosimo-project.com) is available on any digital device using a web browser and takes less than 10 minutes to complete. Participants watch brief muted video clips of dyadic interactions and assign one out of three provided emotional attributes to describe one of the characters. Norm data is available in English and German (N = 1181 spread across two test versions and languages) and 31 PWE have thus far been tested using COSIMO.
Results: In a validation study with N = 18 PWE and N = 27 healthy controls, we found a correlation of r = .64 between COSIMO results and correct answers in a highly sensitive test of social cognition (Dziobek et al. J Autism Dev Disord 2006;36:623-636). Additionally, a significant difference in COSIMO score was found between a control (N = 25) and PWE (N = 31)

group (Hedge's g = 0.87, p = *.002*).
Conclusion: These initial results indicate that COSIMO is a useful tool in screening for social cognition in the majority of PWE. The short time required and easy-to-use online format lowers the threshold for including social cognition in the neuropsychological diagnostics of PWE. The development of COSIMO is supported by the Swiss Foundation for Epilepsy.

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Stress phenotypes in drug-resistant epilepsy: impact on cognitive functioning and quality of life

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Purpose: To establish whether phenotypes according to the stressful life event of epilepsy are related to differences in memory, executive functioning, and quality of life (QOL) in patients.
Method: 170 patients (82 men and 88 women; mean age = 38.21, SD = 11.20) underwent a neuropsychological evaluation in which negative affectivity (trait anxiety and depression), memory, executive function, and QOL were assessed. Hierarchical clustering was performed using z-scores for trait anxiety and depression, as indicators of intensity of stress; and epilepsy duration, as a measure of the chronicity of the stressor. Then, Univariate ANOVAs were performed to determine whether these clusters differed for memory, executive function, and QOL.
Results: Three clusters were found: vulnerable (high negative affectivity and short duration; n=45); resilient (moderate negative affectivity and long duration; n=47); and control group (low negative affectivity and short duration; n=78). The vulnerable group had poorer scores in all memory (for all, $p \leq 0.04$) and QOL subscales (for all, $p \leq 0.005$) than the controls. Furthermore, the vulnerable group had lower scores than the resilient group in executive functioning (for all, $p < 0.03$) and QOL variables (for all, $p \leq 0.03$, except for overall QOL, seizure worry and energy, where no differences were found). Finally, resilient patients had better scores than the control group on executive functioning variables (for all, $p < 0.05$), but lower scores on some QOL subscales (i.e., overall QOL, emotional well-being, and energy; for all, $p \leq 0.02$).
Conclusion: These results suggest that dealing with stress in patients with epilepsy is related to cognitive performance and QOL. These findings may be useful for detecting vulnerable or resilient profiles and for implementing individualized clinical treatments that are better adjusted to the needs of patients.

This work was supported by the project PID2020-118992RB-I00 funded by MCIN/AEI/10.13039/501100011033. J.C.A. was supported by the Generalitat Valenciana (Valencian Government) under grant [number ACIF/2021/094].

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Emotional phenotypes in drug-resistant epilepsy: effects on cortisol levels and memory performance

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Purpose: To determine whether phenotypes according to negative affectivity (i.e., anxiety and depression) are related to the cortisol response to a neuropsychological assessment. Furthermore, it was aimed to determine whether these phenotypes differed in memory performance and in their relationship to cortisol levels.
Method: 135 patients (67 men and 68 women; mean age=37.80, SD=11.30) underwent a neuropsychological evaluation in which cortisol levels were measured at 9 different times. Hierarchical clustering was performed to group patients using z-scores for trait anxiety and depression. To determine whether there were differences between cluster groups, repeated measures ANOVA and *t*-tests for independent samples for cortisol levels and memory scores, respectively, were performed. Furthermore, Pearson correlations were carried out to examine possible relationships between cortisol levels and memory performance depending on these groups.
Results: Two clusters were found: the low negative affect cluster (n=66), and the high negative affect cluster (n=69). Both groups showed the same trend of decreasing cortisol levels as the assessment progressed, but the low negative affect group showed higher cortisol levels (p=0.021). and higher verbal memory scores (for all, p<0.02) than the high negative affect group. In addition, all cortisol levels measured in several time points were negatively related to memory scores only in the low negative affect, except for the first three measures, where no significant correlations were found.
Conclusion: The results suggest a differential impact depending on negative affect on cortisol levels, memory performance and the relationship between them. Negative affect seems to be a relevant variable for clinical decision making due to its comprehensive effect on people with drug-resistant epilepsy, although the basis of the relationship between emotional, hormonal, and cognitive variables remains to be clarified.

This work was supported by the project PID2020-118992RB-I00 funded by MCIN/AEI/10.13039/501100011033. J.C.A. was supported by the Generalitat Valenciana (Valencian Government) under grant [number ACIF/2021/094].

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Working memory impairments in patients with mesial temporal lobe epilepsy

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Purpose: Epilepsy is one of the neurological diseases affecting entire cognitive functioning. In patients with mesial temporal lobe epilepsy (MTLE), language and memory disorders are frequently present, because of the location of the epileptic focus. Considering the impact of epilepsy on the entire neural system, it has been called the "network disease", therefore, it can be assumed that potential deficits may result from the entire brain. For this reason, we decided to go beyond the standard diagnostic scheme and focus on the assessment of a function that is not typically associated with the functions of the temporal lobe. The aim of the study was to assess working memory in patients with MTLE.
Method: Twenty-five patients with MTLE and twenty-five demographically matched healthy volunteers were examined with a set of neuropsychological tests. The general level of functioning (MoCA) and various aspects of working memory (CTT, Symbol Span-WMS-IV, Visual Elevator-TEA) were assessed.
Results: Compared with controls, MTLE patients gained significantly lower scores in the MoCA ($p<0.001$) and needed significantly more time ($p<0.001$) in CTT-2. Differences were also found in the Symbol Span ($p=0.002$) and Visual Elevator accuracy ($p=0.009$). A negative correlation was found between the time of suffering from epilepsy and the results of Symbol Span ($p=0.015$) and Visual Elevator ($p=0.047$). Additionally, age of epilepsy onset positively correlated with the number of errors in CTT-2 ($p=0.028$) and Interference Score in CTT-2 ($p=0.017$). In contrast, the average number of seizures had no clear effect on the tests results.
Conclusion: Patients with MTLE have deficits in working memory, which may reduce their ability to process presented information. Health care professionals should take into account the possible limitations of the patient and adjust the way of communication and the amount of information provided to the patient. This can translate into better adherence to medical advice and better treatment outcomes.

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Cognitive impairment and depression in Albanian patients with epilepsy

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Purpose: Epilepsy is a chronic neurologic disorder which is further complicated by neurobehavioral co-morbidities, psychiatric disorders and cognitive impairment. According to the published articles, depression is the most common psychiatric comorbidity in people with epilepsy.This study aims to access cognitive functions and psychiatric disorders in Albanian

people with epilepsy and identifying the possible risk factors.
Method: 50 (27 females and 23 males) patients with epilepsy were enrolled in this study between November 2022 and January 2023. We performed a structured questionnaire containing socio-demographic, clinical and seizure-related data.Mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MoCA) were used to measure cognitive impairment and Beck Depresion Inventory (BDI) to assess depression. Several variables were included: age, sex, age of disease onset, co-morbidities, type of epilepsy, education, frequency of seizures, monotherapy versus politherapy and family history for depression and cognitive deficits.
Results: Most cognitive problems in adult people with epilepsy include memory and attention . The average was respectively 19,10 for MMSE test, 18.32 for MoCA and 13,75 for BDI test. Patients with longer history of disease had lower MMSE scores, and there was no significant difference in MoCA and BDI scores.The use of polytherapy in the treatment of epilepsy showed higher risk for cognitive impairment (46%) but there was no significant difference in BDI scores.Family history for depression and dementia had a significant impact in the results.
Conclusion: People with epilepsy frequently have cognitive impairment, which is influenced by early onset of epilepsy, duration and frequency of seizures, head injury, anxiety, depression and antiepileptic treatment.Depression is more likely to occur in patients with poorly controlled epilepsy, partial seizures and in those with family history of depression.Further research is needed to investigate significant factors about the cognitive impairment in epilepsy and to routinely screen for depression and treat on time in order to improve their quality of life.

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Academic and labor insertion as a protective factor: effects on negative affectivity and quality of life and their relationship with cortisol levels in a sample of patients with drug-resistant epilepsy

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Purpose: To analyze the possible effect in negative affectivity and quality of life (QOL) depending on academic/employment insertion and to examine the relationship between negative affect and cortisol levels measured during a neuropsychological evaluation in a sample of patients with epilepsy.
Method: 135 patients (67 men and 68 women; mean age=37.80, SD= 11.30) performed a neuropsychological assessment, where cortisol levels were measured in 9 different times. Patients were divided into two groups: with (n=70) or without (n=65) academic/employment insertion. Repeated measures ANOVA was performed to analyze differences in cortisol levels

between groups and t-tests for independent samples to study differences in negative affectivity (depression and trait anxiety) and quality of life. To determine the relationship between cortisol levels depending on insertion, Pearson correlations were carried out.
Results: The results show lower scores in negative affective (p = 0.046) and higher QOL (p = 0.008) in patients with academic/employment insertion than in the inactive group. Likewise, the results point to differences in evening cortisol levels between groups, with higher levels in patients with insertion (p = 0.032) and higher total cortisol production (p = 0.048) than in the inactive group.
Conclusion: Taken together, these results suggest that academic/employment insertion could be a protective factor against negative affectivity in patients with drug-resistant epilepsy, they also showing higher cortisol levels than the inactive group. This fact reaffirms the need to continue investigating the possible response of the hypothalamic-pituitary-adrenal axis to the neuropsychological evaluation in this clinical population, model of chronic stress in humans.

This work was supported by the project PID2020-118992RB-I00 funded by MCIN/AEI/10.13039/501100011033. P.T.P. was supported by grant PRE2021-098237 funded by MCIN/AEI/ 10.13039/501100011033.

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Multiple neuro-developmental disorders associated with a variant of Dandy-Walker Syndrome

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Purpose: Dandy-Walker syndrome is a rare, congenital, genetic malformation of the brain, which affects the posterior cranial fossa, including the cerebellum. This title covers the classical form, Dandy-Walker malformation (DWM) and other milder variants. The incidence of Dandy-Walker malformation is approximately 1 in 25,000 to 35,000 live births. Approximately 50% of children with Dandy-Walker malformations have normal cognitive development, linked to normal vermian lobulation. Lesions of the cerebellar vermis are independent predictors of delay in expressive language and gross motor skills. Malformations of the cerebellum may result in receptive, expressive or mixed receptive-expressive speech disorders.
Method: We present a 3-year-old boy with no perinatal risk factors, and an unremarkable family history, with multiple neuro-developmental disorders, especially speech development, associated with a variant of Dandy-Walker.
Results: Brain MRI showed slight asymmetry of the lateral ventricles, an enlarged IV cerebral ventricle, communicating with an enlarged cisterna magna, low insertion of the tentorium, and inferior vermian hypoplasia. EEG showed non-specific changes. The results of psychological testing indicated attention and concentration disorder, hyperactivity and impulsiveness,

and occasional aggressive behaviour. Examination by a speech therapist showed delayed speech development, more on the expressive than the receptive level. The boy was undergoing early intervention treatment to promote linguistic development and resolve undesirable behaviour, continuous educational rehabilitation and speech therapy, and physical therapy, with reduced screen time and inclusion in kindergarten.
Conclusion: Through this presentation we sought to point out this rare brain development anomaly which should be considered in the differential diagnosis of children with developmental disorders, hyperactivity, aggressiveness and motor clumsiness. This condition requires a detailed and comprehensive family history, detailed clinical and neurological examinations, and mandatory brain imaging. Treatment, requires a multidisciplinary team including a physiotherapist, a speech therapist, a behavioural therapist and a special education expert.

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Long-term intellectual outcome after pediatric epilepsy surgery: a systematic review and meta-analysis

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Purpose: In addition to the primary aim of seizure freedom, a key secondary aim of epilepsy surgery is to stabilize and, potentially, to optimize cognitive development. While the efficacy of surgical treatment for seizure control has been established, the trajectory of intellectual functioning following pediatric epilepsy surgery is yet to be delineated.
We systematically reviewed and meta-analyzed the long-term intellectual outcomes of children and adolescents undergoing epilepsy surgery.
Method: We conducted a systematic review of electronic databases according to the PRISMA guidelines. We included studies reporting pre- and postsurgical intelligence or developmental quotients (IQ/DQ) of patients with focal lesional epilepsy aged ≤18 years at epilepsy surgery and assessed at ≥ 2 years after surgery. We conducted random-effects meta-analysis to determine the mean post- to presurgical change in IQ/DQ and meta-regression to assess predictors of this change.
Results: We included 15 studies reporting on 355 patients for analysis. Mean age at surgery was 5.6 years (range 0.3–13.8). Mean postsurgical follow-up duration was 4.8 years (range 2.7–12.8). The overall estimate of presurgical IQ/DQ was 60 (CI: 47–73) and of postsurgical IQ/DQ 61 (CI: 48–73). We identified a statistically significant, though not clinically relevant, positive post- to presurgical IQ/DQ change (0.94; CI: -1.70–3.58; $p = 0.017$).
Conclusion: Our findings indicate an overall stabilization of intellectual functioning at long-term follow-up after epilepsy surgery. ASM withdrawal, once seizure freedom has been

achieved, enables the optimization of intellectual trajectories in affected children and adolescents.

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The cognitive profile of different idiopathic generalized epilepsy syndromes in adult patients

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Purpose: To characterize the cognitive profile of Idiopathic Generalized Epilepsy (IGE) adult patients, focusing on different syndromic types and exploring the influence of clinical course on neuropsychological outcome.
Method: An extensive neuropsychological evaluation was performed on 47 adult IGE patients (29 female, mean age 40,8 years-old) with a mean follow-up of 9 years, and 21 healthy controls (12 female, mean age 33,3 year-old). IGE patients were characterized according to syndromic types (Generalized Tonic-Clonic seizures Alone GTCA, 15 patients, Juvenile Myoclonic Epilepsy JME 16, Juvenile Absence Epilepsy JAE 16) and prognosis (persistence of seizure during the follow-up, drug-resistance, number of antiseizure medication -ASMs- at the cognitive assessment). Statistical analysis: Kruscal Wallis test for the association between categorical variables; in case of significance, Dunnett test with Bonferroni correction for multiple comparisons, as post hoc analysis.
Results: IGE patients performed significantly worse compared to controls in all domains explored. JME and JAE showed a significantly worse clinical course. Considering different IGE types compared to controls, all IGE types performed worse on long-term memory and attention; JME showed greater deficit in executive functions, JAE also in visuo-spatial abilities. Both JME and JAE performed significantly worse on global cognition. Seizure persistence throughout follow-up was associated with worse performance on global cognition, executive functions, and visuo-spatial abilities. Drug-resistant patients and those with a higher number of ASM at the cognitive assessment additionally showed deficits in working memory, attention and speed processing. Age at seizure onset did not affect the cognitive performance assessed in adulthood in this group of patients.
Conclusion: Subtle differences between cognitive profiles of different IGE syndromes further suggest different constitutive neuronal networks to be explored. A worse clinical course, often associated with an increased pharmacological burden, adds specific cognitive deficits that should be identified for a better management of the patient.

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Evaluation of the quality of life of epileptic patients: descriptive and analytical cross-sectional study of a Tunisian series

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Purpose: This work is aimed at determining the epidemiological, clinical and therapeutic characteristics of epileptic patients in the region of Mahdia, evaluating their quality of life and determining the associated factors that may alter it.
Method: We conducted a descriptive and analytical cross-sectional study of a cohort of 71 patients treated for epilepsy at the outpatient Neurology Department at Tahar SFAR University Hospital in Mahdia.
Results: We collected 71 patients (41 males and 30 females). The mean age was 36.08 years with extremes of 18 and 80 years. Parental consanguinity was found in 31% patients. 70.4% of patients had a primary school level and 53.5% were single. Quality of life was measured using the SF36 generic scale (Short-Form) in its validated literaryArabic version. It concluded that 63.8% of patients had impaired QOL. Screening for a possible depression was done using the PHQ-9 scale (valitaded version) and 74.6% of the patients had depression ranging from mild to severe. The evaluation of cognitive functions was performed using the MOCA scale designed for the evaluation of mild cognitive dysfunction. It revealed that 70% of patients had mild cognitive impairment. In correlation with the SF36 scale, the factors found to be involved in the deterioration of quality of life were : the absence of a professional activity, the educational level, low socio-economic level, poor response to treatment, polytherapy, the presence of depression and the frequency of seizures.
Conclusion: The systematic use of screening tools for anxiety and depression disorders can help identify at-risk epileptic patients while helping the follow-up of their symptoms during subsequent visits. A good communication between the doctor and the patient is necessary for a better therapeutic observance and therefore a reduction in the frequency of the crises to ensure a better management and quality of life.

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Retrospective insights into childhood epilepsy

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Purpose: Although many children who experience epilepsy in childhood enter remission, childhood epilepsy may have psychosocial effects that can prove enduring throughout childhood and adulthood. While the long-term effects of childhood epilepsy have been examined extensively using objective measures such as educational attainment and employment rates,

less is known of the subjective lived experience of epilepsy as recalled in adulthood. The aim of this study was to capture adults' retrospective insights into the impact of epilepsy during childhood.
Method: Participants were 13 Irish adults aged 18 and 35 years, who had their first seizure on or before the age of 16 years. Participants self-referred to the study via social media and epilepsy support agencies. A semi-structured interview schedule was developed to explore participants' understandings of epilepsy and experiences of epilepsy supports during childhood. Reflexive thematic analysis was used to analyse interviews.
Results: Interview data generated three main themes. These themes comprised (1) disenfranchised grief, (2) the need to belong and (3) meeting each child at their individual level. Participants reflected that the diagnosis of epilepsy in childhood evoked a grief response which only those with epilepsy could experience. Participants also recalled feeling isolated by their epilepsy as children, although the support of friends and family ameliorated these feelings. Finally, participants suggested that developmentally appropriate practices might be adopted in educational and clinical settings to foster greater understandings of epilepsy amongst young people.
Conclusion: This study suggests that effective support of children with epilepsy across educational and clinical settings must take the child's emotional and developmental standing into consideration. Reflections highlight participants' poor understanding of epilepsy during childhood, in addition to a failure by stakeholders to acknowledge the feelings of the child. This study reiterates the importance of meaningfully including young people with epilepsy in their own treatment and care.

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Cognitive dysfunction and brain connectivity at epilepsy onset: detecting changes at the early stages of disease

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Purpose: Cognitive dysfunction and disruptions in brain connectivity have been correlated with seizure control in chronic epilepsy and in newly diagnosed epilepsy, which potentially makes them good markers for predicting disease course and seizure control. However, there is a lack of prospective studies in individuals at the earliest stages of the disease, such as following the first unprovoked seizure (UFS) or new onset epilepsy (NOE).
Method: To date, nineteen adult participants with FS (n=8) and NOE (n=11) from the Halifax First Seizure Clinic completed a cognitive screening assessment and resting state fMRI to evaluate functional connectivity.

Results: Cognitive impairment, defined as at least one Z-score in the impaired range ≤-1.5, 7th percentile, was present in 88% of patients, which is higher than expected by chance in a healthy population (31.4%). Most patients with obtained global cognitive Z-scores below 0 (mean -0.51, std 0.39), reflecting mild but significant cognitive dysfunction relative population norms (t=-3.9, p<0.05). rsfMRI analyses focused on the default mode network (DMN) and showed differences between patients and age-matched healthy controls in local efficiency in the right and left medial frontal nodes with effect sizes of d=1.5 and 1.08, respectively, and in clustering coefficient in both of these nodes with effect sizes of d=1.5 and d=1.0, respectively.
Conclusion: Subtle changes in cognitive function and functional brain connectivity are detectable in early stages of epilepsy. This link suggests that these factors warrant further investigation as potential biomarkers for tracking clinical course and seizure recurrence.

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Social cognition and quality of life in patients with drug resistant temporal lobe epilepsy

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Purpose: As numerous studies show, patients with drug-resistant epilepsy have a significantly reduced quality of life (QoL). The quality of life is influenced by many factors, including health and mood, but also the quality of interpersonal relationships. The ability to establish close and satisfying relationships is in turn related to the person's social competences. The study aimed at assessing social cognition skills in patients with intractable epilepsy and evaluating its impact on their QoL.
Method: The clinical group consisted of 80 subjects with drug resistant temporal lobe epilepsy: 40 women and 40 men in the mean age of 31,41 ± 9,78 and 14.01 ± 3.22 years of education. The average duration of epilepsy was 19 ± 6,98 years. The control group consisting of healthy volunteers (n=80) was demographically matched. The neuropsychological examination was conducted using a set of tests evaluating the quality of life (QOLIE-31-P) as well as social cognition competences: recognition of emotions (RMET) and recognizing intentions based on observation of body movements (CID-5). The level of depression and anxiety was controlled using the HADS scale.
Results: The group of patients with epilepsy achieved significantly lower scores than healthy controls in all measures of social cognition (p<0,05). Further analysis revealed significant positive correlation between QoL scores and RMET (r = 0,61; p<0,05), as with CID-5 (interaction recognition: r = 0,73; p<0,05; interaction naming: r = 0,38; p<0,05) and negative correlation between QoL and depression subscale of HADS (r = -0,61; p<0,05).
Conclusion: The level of quality of life as measured with the use of QOLIE-31-P is related with social cognition deficits and depression. Patients with epilepsy should be provided with special care including the therapy of social cognitive disorders and training of social competences

because its deficits can lower their quality of life and increase a risk of depression.

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A juvenile with dissociative seizures mimicking oculogyric crisis: an unusual case report of eye sign of conversion disorder

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Purpose: Dissociative seizures is very similar to epileptic seizures. Approximately one third of persons with dissociative seizures are misdiagnosed as epileptic seizures. The differential diagnosis of dissociative seizures and epileptic seizures is an ongoing challenge. We reported a juvenile with a 3-month history of episodic upward strabismus with body twitching (oculogyric crisis-like). Although the manifestations of dissociative seizures are diverse, a dissociative seizures mimicking oculogyric crisis is rare, which may be the first report.
Method: To confirm the diagnosis, we conducted a physical examination, laboratory tests of blood and cerebrospinal fluid, head imaging, video-electroencephalogram (VEEG) monitoring, and psychological evaluation for the patient.
Results: Laboratory tests and head imaging were negative, psychological evaluation suggested moderate depression tendency, and no epileptic discharges were detected during either ictal or interictal period of VEEG monitoring.
Conclusion: Finally, the patient was diagnosed with dissociative seizures and psychological treatment was carried out. From the case, we review how to identify dissociative seizures as early as possible.

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The neuropsychological profile of the patients with drug-resistant epilepsy: a study of Moldovan population

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Purpose: To establish the cognitive, affective, and behavioral characteristics of patients with drug-resistant epilepsy and to realize a neuropsychological profile.
Method: 62 patients with drug-resistant epilepsy were evaluated, aged 18-62 years (mean age =34,4 years, ±10,2 years, mean epilepsy duration=21,7 years ± 9,9 years). The neuropsychological tests applied: MoCA, RAVLT, ROCF, Trail making test, COWAT, BDI, HAM-A, BDHI, RCBS-13. The study took place at National Center of Epileptology, Chisinau, Republic of Mol-

dova in 2022.
Results: This study has demonstrated that 61% of patients with drug-resistant epilepsy have cognitive impairments: 56% suffer from depression and 53% from anxiety. Also, we noticed an everage shyness in 58% and a high shyness in 15%. As well, high hostility in 60% of the patients and a high aggressivity in only 2%. Corelations analyses of cognitive, affective and behavioral test, revealed that the cognitive domains presented by visual memory, verbal memory, phonemic and category fluency, visual-constructive skills, attention and mental flexibility are significantly affected by depression (r=-0,22), anxiety (r=-0,16) and shyness (r=-0,34). Therefore, the better the cognitive domain is, the lower is the level of shyness, anxiety, depression and aggression. It was demonstrated that, the higher the level of anxiety and depression is, the higher it is the level of shyness (r=0,38), aggression (r=0,37), and hostility (r=0,39). At the same time, the high level of depression and anxiety is inversely proportional to the cognitive domain, in particular visual-constructive skills (r=-0,23) and attention (r=-0,24). In addition, aggressiveness, hostility and mainly shyness is more pronounced in patients with severe cognitive disorders.
Conclusion: Our results suggest a specific neurocognitive profile of the patient with drug-resistant epilepsy. The neuropsychological features are: decreased verbal and visual memory, slowed thinking and processing speed, impaired attention and difficulties in identifying words; depression, anxiety, hostility, resentment, feelings of guilt and shyness.

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Patients with epilepsy with myoclono-atonic epilepsy show early attention and executive dysfunctions

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Purpose: Executive functions and attention (EFA) have a major influence on quality of life, social skills and school success. Preschool ages are a key time period in their development. Executive complaints in patients with epilepsy with myoclonic atonic seizures (EMAtS) in preschool ages were previously reported using parental questionnaires. This study aims to evaluate EFA in preschool children with EMAtS using specific and adapted tools and to correlate this evaluation with epilepsy characteristics.
Method: We included two groups of children aged from 3 to 7 years old: a group of EMAtS patients and a group of typically developing children (TDC). We developed a battery of cognitive tests targeting EFA. Demographic and medical data were collected (age at seizure onset, seizure frequency, number and type of antiseizure medication, time to response to treat-

ment, …).
Results: We recruited 22 EMAtS and 67 TDC children. Group comparison shows significant differences with lower scores for EMAtS on inhibition, working memory, selective and sustained attention tests. Performance on EFA tests are linked to ASM type, seizure frequency and time to response to treatment. Patients with longer response to treatment show more EFA difficulties.
Conclusion: We confirm the possibility to detect dysfunctions in EFA in children with EMAtS in preschool ages. Dysfunctions are linked to ASM and the evolution of the disease. Results highlight the necessity of precocious and prospective evaluation targeting EFA in EMAtS children.

Neurostimulation

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The specifics of providing medical care to children with epilepsy during military actions on the territory of Ukraine

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Purpose: To study the specifics of providing medical care to children with epilepsy during martial law
Method: We conducted a survey of parents of 108 children with epilepsy aged from 1 to 18 years, 62 boys and 46 girls. The data were obtained through an anonymous online questionnaire. The results are processed statistically
Results: 8.33% of children were in temporarily occupied regions of the country for a certain period of time, 52.78% were direct witnesses of combat and/or other military actions. 103 children at the time of examination were constantly taking AED. In 10.19% of patients during the war occurred a break in the remission of attacks. Among its causes, the parents noted: stress - in 45.45%, forced replacement of AED - in 27.27%, infectious diseases - in 27.27%. Among patients without remission, an increase in the frequency of attacks was noted in 31.11%. Parents of 87.96% of patients reported that the child continued to receive necessary medical care during the war, 71.30% found adequate contact with a doctor in Ukraine, and 18.52% received/are receiving medical care in other countries.
Problems with access to laboratory (25.99%) and instrumental (25.93%) examination methods were identified.
But the most significant problem turned out to be the provision of AED. 50.49% of parents reported difficulties with obtaining drugs during the war at budgetary expense, and in 48.54% of cases there were difficulties with purchasing drugs in the pharmacy network at their own

expense
Conclusion: According to parents opinion, the main reasons for disruptions in drug remission of seizures are: stress, forced replacement of AED, infectious diseases.
In most cases (87.96%), parents noted a satisfactory level of providing medical care to their children.
Parents of about 50% of patiecnts indicate problems with obtaining AED

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Transcutaneous auricular vagus nerve stimulation (ta-VNS) for treatment of drug-resistant epilepsy: a randomized, double-blind clinical trial

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Purpose: To explore the efficacy and safety of transcutaneous auricular vagus nerve stimulation (ta-VNS) in patients with drug-resistant epilepsy.
Method: A total of 150 patients were randomly divided into active stimulation group (n=100 and control group (n=50). At baseline and 4, 12, 20 weeks of stimulation, demographic information, seizure frequency, adverse events were recorded; at 20 weeks, the patients underwent assessment of quality of life, Hamilton Anxiety and Depression scale, MINI suicide scale and MoCA scale. Seizure frequency was determined according to the patient's seizure diary. Seizure frequency reduction > 50% was considered as effective. During our study, the antiepileptic drugs were maintained at a constant level in all subjects.
Results: At 20 weeks, the responder rate was significantly higher in active group than in control group. The relative reduction of seizure frequency in the active group was significantly higher than that in the control group at 20 weeks. Additionally, no significant differences were shown in QOL, HAMA, HAMD, MINI and MoCA score at 20 weeks. The main adverse events were pain, sleep disturbance, flu-like symptoms and local skin discomfort. No severe adverse events were reported in active and control group. There were no significant differences in adverse events and severe adverse events between the two groups.
Conclusion: In view of the significant higher responder rate along with no significant increase in adverse events, the present study showed that ta-VNS is an effective and safe therapy for epilepsy. Furthermore, the benefit in QOL and neuropsychological state of ta-VNS need further validation in the future study although no significant improvement was shown in this study. We believe that ta-VNS may be a promising non-invasive treatment options for patients with epilepsy, especially for those resistant to ASMs.

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Personalized identification of neural oscillations via data-driven models of the epi-

leptic network dynamics

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Purpose: Neural oscillations fundamentally contribute to the understanding of the brain functioning. When these oscillations are altered, they can lead to impaired brain functions, such as seizures in epilepsy patients. Indeed, the analysis of temporal and spatial properties of the different brain rhythms in the epileptic network is the basis for medical diagnosis and forecasting, where it becomes crucial to correctly identify patient-specific characteristics. However, both clinical and scientific considerations are often restricted to generalized assumptions on typical anatomical and neurophysiological features.
Method: We develop a method for a personalized determination of dominant coherent brain oscillations, based on EEG recordings. A data-driven model is used to capture the effective dynamical connectivity matrix of the steady-state EEG dynamics. The population of interest consists of epilepsy patients. Both non-ictal EEG activity as well as recordings of patients in status epilepticus are included, as contrasting examples of steady-state dynamics.
Results: We determine the spectral and spatial properties of the endogenous brain oscillations, in a patient-specific and assumption-free manner. In addition, the model-based approach allows anticipating the different responses in novel treatments of drug-resistant cases of epilepsy via brain stimulation.
Conclusion: We developed personalized models for the identification of endogenous brain oscillations, based on EEG recordings of epilepsy patients. In contrast to standard spectral analyses, the approach distinguishes persistent coherent oscillations from accidental noisy dynamics. The identified oscillations, as well as their responsiveness to different stimulation frequencies and locations, can be used to guide novel brain stimulation paradigms.

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Longitudinal assessment of executive functions following vagus nerve stimulation therapy by using EpiTrack in patients with drug-resistant epilepsy

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Purpose: To investigate executive functions and attention with repeated EpiTrack evaluations in a group of drug resistant epilepsy (DRE) patients receiving vagus nerve stimulation (VNS) therapy during a follow-up time up to five years.
Method: The study group consisted of 33 DRE patients (19 females and 14 males) with a median age of 32 years (interquartile range: 27-41) who were assessed with EpiTrack as a part of clinical VNS-protocol. Scheduled evaluations according to our protocol were firstly done prior

to VNS-implantation, thereafter at 6 months, 12 months and after that yearly. However, due to covid-19 pandemic, these visits did not always take place. Therefore, changes in EpiTrack total scores over time were analyzed using a semiparametric generalized estimating equation model to compensate for the variation in time predicting EpiTrack total score change per month during a period of 60 months.
Results: The key finding of our study was that the EpiTrack total score was significantly improved during the follow-up time in a group level. During each month, on average, EpiTrack total score was increased by 0.07 units (estimate 0.07, 95% CI 0.01 to 0.12, p = 0.016). Another substantial finding was that in the group of patients with psychiatric comorbidities, the EpiTrack total score significantly increased on average 0.14 units per month (estimate 0.14, 95% CI 0.049 to 0.23, p = 0.003), and that increase was twofold when compared to the whole study population.
Conclusion: A clinically meaningful improvement was observed, representing a change of more than one standard deviation, on executive functions of DRE patients during the five years after the initiation of VNS-therapy. DRE patients who had depression as a comorbidity, seemed to benefit cognitively the most on VNS-therapy.

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Vagus nerve stimulation: clinical and technical data for the patient's selection

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Purpose: Defining best parameters for the selection of the candidates to VNS.
Method: Among the patients implanted for DRE with VNS at our Centers we collected 36. Inclusion criteria: age at the implant (AI) before 18 years and accurate follow-up (outcomes -McHugh scale-, Total Charge (TC), Current (C), Duty Cycle (DC,) AI, time of the epilepsy before the implant (TE), follow-up (FU). We stratified 3 subsamples: A) AI< 5 versus AI>6 years; B) TE< 5 versus TE>6 years, C) outcome I versus outcome III-V.
Results: Whole Sample: 36 patients, AI 9,1 years, TE 7,4 years ,FU 7,1 years. ClassI 16 pts (6 seizure free), ClassII 11 ClassIII-V 9. The mean stimulation parameter (SP) were: TC 189,2 mC., C 1,8 mA, DC 14%.
A) AI < 5: 9 patients (TE 2 years); ClassI 9 patients. SP: TC 185,99 mC, C 1,75 mA and DC 15,33%. AI > 6: 27 patients, AI 11,2 years, TE of 9,2 years FU of 5,1 years. SP: TC 190,56 mC, C 1,8 and DC 13,56%. The outcomes were: ClassI 7, ClassII 11, ClassIII 3 ClassIV 1 ClassV 5 pts.
B) TE<5 years: 15 patients, TE 2,88 years, FU of 8 years; ClassI 15 patients. SP: TC 193,3 mC, C 1,77 mA and DC 15,6%. TE > 6 years: 21 patients, AI 12 years, TE 10,6 years FU of 7 years. SP: TC 186,2 mC, C1,8 and DC 12.9%. Outcomes: ClassI 5, ClassII 7, ClassIII 3, ClassIV 1 and ClassV 5 patient.
C) (SR versus NR). SP: there were no significative differences in the stimulation parameters (DC 166,25/174,21mC, C 1,7/1,64 mA and DC 14,5/12,4 %) between the two groups
Conclusion: Only AI< 5 years (TestT 0,004) and TE< 5 years (TestT 0,00057) seem to correlate

with best outcomes. No specific dosing seem clearly correlate with outcomes.

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Prediction of vagal nerve stimulation based on invasive EEG analysis in drug-resistant epilepsy

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Purpose: Vagal nerve stimulation (VNS) represents a therapeutic option in patients treated for drug-resistant epilepsy. VNS significantly reduce seizure frequency in 50-60 % of patients (responders). In the resting patients, VNS has only minimal impact on seizure numbers (non-responders). By now, we are not able to predict reliable VNS efficacy before its implantation. In the presented study, we focused on the VNS efficacy prediction based on invasive EEG (SEEG) analysis
Method: We retrospectively reviewed epilepsy patients undergoing SEEG for drug-resistant focal epilepsy. We identified patients implanted with VNS, because SEEG data were insufficient for surgery delineation or surgery did not lead to seizure cessation. VNS patients were categorized as responders (≥ 50% seizure reduction) or non-responders (< 50 % seizure reduction). We compared VNS responders and non-responders based on number or interictal epileptiform discharges (IEDs) and high frequency oscillations (HFOs) in seizure-onset zone (SOZ) and non-seizure onset zone (non-SOZ). As the last step, the classifier based on machine learning using support vector machines was developed.
Results: We identified 20 patients with SEEG who subsequently underwent VNS implantation – 9 responders, 11 non-responders. Responder and non-responders did not differ significantly neither in IEDs, nor HFO frequency in SOZ and non-SOZ, respectively. We constructed a classifier, which was capable to predict VNS efficacy with sufficient accuracy (0,8 accuracy for both SOZ and non-SOZ).
Conclusion: The SEEG data could be applied in prediction of VNS response. This approach could be potentially helpful in some patients ´groups.

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ANT-DBS in refractory epilepsy: a single-center experience

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Purpose: Deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) is an evidence-based, third line treatment for patients with drug-resistant epilepsy (DRE). We report the experience of a single center.
Method: We retrospectively studied clinical outcome in 22 consecutive DRE patients treated with ANT-DBS. Patients were encouraged to keep seizure diaries. Other aspects were monitored during regular clinical interviews.
Results: We implanted 21 patients with bilateral electrodes in the ANT using transventricular trajectories if venous anatomy allowed a safe transventricular corridor (38/42 leads). Four patients were lost to follow up, one was implanted at another center. The median follow-up time was 52 months (range 1-84 months). Stimulation parameters and anti-seizure medications were adjusted according to clinical standards. Fourteen patients kept seizure diaries and reported a median change in total seizure frequency of -73.4% (range -41.5%- -96.1%) with a responder rate (>50% reduction in seizure frequency) of 85.7% at last follow-up. Five out of seven patients without a seizure diary reported a significant improvement. Seizure severity was reduced in seven, remained similar in four and increased in three patients. Two patients reported a longer postictal period. Eight patients felt better than before DBS treatment. Two patients reported a positive effect on cognition. There was only one patient who was admitted to treat a potential infection because of poor wound healing, without the need of hardware removal. Six patients reported hinderance due to the subcutaneous cables or the battery, which improved over time. Four patients reported reversible stimulation-related side effects, which disappeared when stimulation parameters were adjusted. Four patients reported memory impairment.
Conclusion: ANT-DBS is a safe treatment and can be successfully implemented as a third line treatment for DRE. Besides changes in seizure frequency, duration and severity, cognitive effects are important contributors for quality-of-life in these patients.

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A global survey of practice habits for the management of vagus nerve stimulation therapy

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Purpose: Vagus Nerve Stimulation (VNS) Therapy has been a widely adopted therapy for drug-resistant epilepsy (DRE) for several decades. However, the paucity of evidence-based

recommendations for VNS dosing and titration has led to variability in practical implementation of VNS around the globe.
Method: A survey was developed to assess VNS dosing and titration behaviors amongst healthcare professionals (HCPs) treating patients with DRE. HCPs who routinely manage patients with DRE were invited to take part in this survey either by email or at one of two epilepsy congresses in Europe and North America.
Results: As of December 2022, 135 responses have been collected from largely Western European and North American HCPs (110/135; 81.5%). Most reported using at least one neuromodulation modality for treatment of DRE in their clinical practice (120/135; 88.9%), with the majority using VNS only (65/120; 54.2%). Of the 93 respondents responsible for VNS programming, the median output current range was 1.50mA to 2.50mA; however, there was significant variability in responses and some users reported programming VNS output currents well below the manufacturer's recommendation. The most commonly used pulse width and frequency used were 250µsec (61/93; 65.6%) and 20 Hz (48/93; 51.6%), respectively. On average, HCPs stated that they reach their preferred target dose within 9.18 weeks (range 1 to 56 weeks). Respondents report assessing the impact of VNS at approximately 5 months after achieving the perceived target dose range. Some users had access to VNS devices with novel features including AutoStim and Scheduled Programming. The majority of VNS users with access to these features reported using them frequently, with 79.5% reporting using AutoStim and 51.4% using Scheduled Programming in most of their patients.
Conclusion: While VNS management mostly follows the manufacturer's recommendations for use, individual VNS users may have highly variable dosing and titration approaches.

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Investigational microburst vagus nerve stimulation: safety and efficacy outcomes

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Purpose: New vagus nerve stimulator settings called "microburst stimulation" (µVNS) with high-frequency bursts of 100-350 Hz have been investigated in humans hypothesizing that µVNS may be more tolerable and efficacious than standard VNS therapy.
Method: This prospective, unblinded multicenter study aimed to recruit 2 cohorts of 20 pa-

tients each, age ≥12 years, with either drug-resistant focal (FE) or any generalized epilepsy with tonic-clonic convulsions (GE). Enrolled subjects underwent implantation of the investigational M1000C VNS device and 4 functional MRIs to titrate settings to µVNS parameters with the most robust thalamic blood-oxygen-level-dependent signal response. Data collected at baseline and during 12-months follow-up (FU) included demographics, seizure frequency, antiseizure medications (ASMs), seizure severity, quality of life in epilepsy and suicidality questionnaires, VNS parameters and adverse events (AE). Primary endpoints were safety and efficacy.
Results: A total of 32 subjects (20 FE and 12 GE) were enrolled. At baseline, patients in both groups were on an average of 3.5 ASMs and previously failed 4-7 ASMs. Regarding outcomes, 2 FE patients were lost to FU and 1 GE patient had device explantation due to high lead impedance. For the total population, ≥50% seizure reduction at 6- and 12-months were 41.9% and 63.3%, respectively. 63.2% of responders (12/19) experienced ≥80% reduction and 4 patients were seizure-free in the final 6 months of FU. At 12-months FU, overall seizure severity was reduced in 70% (21/30) and QOL scores improved. ASM load decreased by 10%. Adverse events affected 1/20 people with FE and 5/12 GE patients.
Conclusion: µVNS therapy appears safe and potentially more efficacious than standard VNS therapy with a similar AE profile. Responders appeared more likely to have ≥80% seizure reduction within the first 12 months with µVNS. Seizure severity, QOL, and ASM load improved after µVNS at 12 months FU. Further prospective studies are warranted.

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One-year seizure-freedom in patients treated with adjunctive VNS therapy in Japan

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Purpose: Efficacy of an ASM/Therapy is typically reported as the fraction of patients experiencing 50% or greater reduction in seizure frequency (responder rate). Vagus nerve stimulation (VNS) is an established therapy for DRE, however, the fraction of patients with VNS experiencing prolonged periods of seizure freedom (SF) has yet to be assessed on a large scale.
Method: This retrospective analysis included a fraction of patients from 52 sites in the Japanese VNS Post Market Registry who underwent VNS implantation (July 2010 and December 2012) with at least one year of SF. Three separate seizure counts were measured: all seizures (AS), focal seizures (FS), and generalized tonic-clonic seizures (GTCS).
Results: After 36 months, the cumulative fraction of patients experiencing at least one year of complete SF was 11% (38/356) (average duration = 19.4 m). Of the 225 patients with FS prior to VNS implantation, 57 (25%) experienced at least one year of SF (average duration = 24.8 m). Higher cumulative rates of freedom from BTCS were observed over 36-months: of 184 patients who experienced BTCS prior to VNS implantation, 101 (55%) experienced at least one year without BTCS (average duration of BTCS-free periods = 28.9 m). When excluding the 25

patients who experienced BTCS prior to VNS, but not in the 3-month baseline period before implantation, 1-year SF from BTCS was experienced by 49% of patients (78/159) with a 79% responder rate at the 36-month visit.
Conclusion: Eleven percent of patients undergoing VNS Therapy had complete SF. Approximately half of patients with BTCS prior to VNS experienced prolonged periods of freedom from BTCS following implantation. This is of interest since many consider BTCS to be their most debilitating seizure type. BTCS has a high association with head-trauma, other seizure-related injuries, and are the main risk factor for sudden unexpected death in epilepsy.

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Vagus nerve stimulation in the elderly and in late-onset epilepsy

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Purpose: The prevalence of epilepsy in the elderly has been shown to be approximately 2%-5%, three to four times higher than in younger adults. Vagus nerve stimulation (VNS) is an established adjunctive therapy for drug-resistant epilepsy (DRE) and recent clinical investigations have focused on its application in pediatric DRE. Data are limited on the use of VNS in the elderly and late-onset epilepsy.
Method: A pooled database of prior VNS studies was analyzed to identify subjects based on age and duration of epilepsy at implant. Only patients receiving VNS Therapy were considered. Seizure rates at baseline were compared to recorded seizure rates at post-implant follow-ups at 3, 6, and 12 months. No data were imputed for missing visits or dropouts.
Results: 247 patients > 40 years of age (yoa) at VNS implantation were identified from 1,191 (21%) possible. At 12 months of VNS Therapy (n=149), 50.3% of patients were defined as responders (> 50% reduction of seizure frequency compared to baseline), median reduction of seizure frequency was 50%. The 12 months responder rates were similar for 40-49 yoa (n=84) and 50-59 yoa (n=45): 48.8% vs 48.9% respectively. A slightly higher responder rate (60%) was seen in patients 60+ yoa at implantation (n=20): median seizure frequency reduction was 56.6% at 12 months. The greatest response was observed in the late-onset epilepsy group (aged 40+ years at epilepsy-onset; n=26, 2.2%): at 12 months (n=16), 68.8% of patients were responders, 31.3% of patients experienced more than 80% seizure frequency reduction, and the median seizure frequency reduction is 66.8%.
Conclusion: The effectiveness of VNS therapy in patients > 40 is at least similar to younger adult patients with VNS. Whether patients with a greater age at implantation or later onset of epilepsy may have better outcomes or have a different long-term neuromodulatory effect warrants further investigation.

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High frequency functional connectivity resembles CCEP-based network in the human mesial temporal lobe in intracerebral EEG

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Purpose: Studies of human brain connectivity received lately growing attention as a topic of high impact in the understanding of both physiological and pathological human brain organization. Neuronal connectivity in vivo based on intracranial EEG signal can be assessed by evaluation of either spontaneous neuronal oscillations or evoked responses. Significant divergence between spontaneous and evoked networks has been reported in several recent studies.
Method: To address the question of resemblance between the networks, we investigated effective and frequency-dependent functional connectivity among the structures of anterior and mesial temporal network including amygdala, hippocampus, temporal pole and parahippocampal gyrus, in the living human brain. Intracranial SEEG recording was obtained from 19 consecutive epilepsy patients with normal anterior mesial temporal MR imaging undergoing intracranial presurgical epilepsy diagnostics with multiple depth electrodes. We assessed intratemporal bidirectional effective connectivity by means of SPES method as well as functional connectivity using several causality measures such as Granger causality (GC), directed transfer function (DTF) and partial directed coherence (PDC) in a frequency-specific way.
Results: The closest overlapping to the evoked network was found for the functional connectivity assessed by the GC method, most prominent in the higher frequency bands (alpha, beta and low gamma), gradually vanishing in the lower frequencies. Functional connectivity assessed by means of DTF and PCD obtained basically a similar directionality pattern with the exception of connectivity between hippocampus and parahippocampal gyrus that appeared to be directed contrariwise.
Conclusion: Our data suggest that both functional and effective methods are suitable for detection of local circuits, however, application of several measures might be necessarily for the validation of results.

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Vagus nerve stimulation in super-refractory status epilepticus: the experience of a tertiary epilepsy center in Italy

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Purpose: Neuromodulation is emerging as a safe strategy to reduce the mortality burden of super-refractory status epilepticus (SRSE). According to a recent review, vagus nerve stimulation (VNS) implantation was associated with RSE/SRSE interruption in 74% (28/38) of cases. Evidence about optimal stimulation parameters is lacking.
Method: We report our clinical experience with VNS treatment for SRSE.
Results: **Case 1** A 16-year-old girl affected by Lafora Disease developed SRSE and underwent VNS implantation on the 66th day after SE onset. Within the 5th post-operative day, the parameters were progressively increased up to intensity 1.75 mA, 30" on-1.8' off. On day 3, sedation was successfully withdrawn, and EEG showed a progressive reduction of seizure activity. Only sporadic GTCS occurred during the next nine months, then she died from tracheostomy-related complications.
Case 2 A 20-year-old boy presented with new onset super-refractory SE (NORSE) in the aftermath of a febrile illness. On the 86th day from SE onset VNS was implanted. Within the 6th post-operative day, the parameters were progressively increased up to intensity 2mA, 30" on-1.8' off. Sedation was interrupted and vigilance gradually recovered. On day 8, after recurrence of SE, the parameters were further modified to intensity 2.25 mA, 30'' on-1.1' off. He presented only isolated seizures for nine months. Afterward, SRSE relapsed.
Case 3 A 25-year-old lady with undiagnosed Medium-Chain Acyl-Coenzyme A Dehydrogenase and past unresponsiveness to VNS manifested SRSE. As a last resort, the VNS battery was replaced, and parameters were rapidly augmented to intensity 1.75 mA, 30" on–1.1' off. After sedation withdrawal, SE recurred, and she eventually died.
Conclusion: In our experience, acute VNS implant and rapid titration to high stimulation parameters has proved to be a safe procedure and, in two out of three cases, played a major role in SE cessation.

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Neuropsychological outcome in focal cortex stimulation for the treatment of patients with refractory focal epilepsy

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Purpose: Focal cortical stimulation by means of EASEE-system is a new neurostimulative approach, which was recently approved in Europe as an effective and safe treatment of refractory focal epilepsy. Due to its applicatoins of cathodal stimulation to achieve antiseizure effects, one can raise concerns about the neuropsychological outcomes. We provide a thorough neu-

ropsychological evaluation of patients treated with focal cortex stimulation in our university center.
Method: In our cohort of 15 patients, we performed neuropsychological tests before the initiation of the focal cortical stimulation and 12 months after. The following neuropsychological assessments were applied: the German version of the Auditory Verbal Learning Test (AVLT), the Welcher Memory Scale (visual reproduction) WSM-IV, the Regensburger Word Fluency Test (RWT), the five-point test (5-PT) and the *Wechsler* Adult Intelligence Scale (WAIS-IV/mosaic test).
Results: The results of the neuropsychological analyses at the 12 month follow up after the initiation of focal cortical stimulation showed a statistically significant improvement of the visuo-spatial- constructive performance, semantic word fluency, short-time memory in visual memory and the figural fluency in comparison tot he test prior to the initiation of stimulation ($p<0.05$).
Conclusion: Focal cortical stimulation by means of EASEE-system improves not only the seizures frequency but may also the overall neuropsychological outcome in patients with refractory focal epilepsy.

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Favourable combinations of vagus nerve stimulation with antiseizure medication

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Purpose: Vagus nerve stimulation (VNS) is a neurostimulative approach, which has been proven to be effective in the treatment of refractory epilepsy. However, favorable combinations of different groups of antiseizure medication (ASM) and VNS have not been yet sufficiently investigated. Our purpose was to evaluate possible synergistic effects between VNS and different ASMs.
Method: In this observational study, we included patients with refractory epilepsy who were implanted with a VNS device and maintained their ASM unchanged during the first two years after the implantation. Data was collected in terms of the Mainz Epilepsy Registry. The efficacy of VNS depending on the adjunctive ASM was estimated by means of the responder rate (≥ 50% seizure reduction compared to the time of VNS implantation) and seizure freedom (absence of seizures during the last six months of the observation period).
Results: We included 151 patients (mean age 45.2 ± 17.0 years, 78 females), who showed a responder rate in the whole cohort of 50.3% and the seizure freedom of 13.9%. The higher responder rate and seizure freedom were shown upon the combination of VNS and synaptic vesicle glycoprotein (SV2A) modulators (responder rate and seizure freedom of 64.0% and 19.8%, correspondingly, both $p < 0.01$) or VNS and slow sodium channel inhibitors (responder

rate and seizure freedom of 61.8% and 19.7%, correspondingly, both $p < 0.01$). Concerning the individual ASMs, brivaracetam showed a more favorable effect than levetiracetam, whereas lacosamide and eslicarbazepine were comparable in their effects.
Conclusion: The results of our study show that the combination of VNS with ASMs acting either via SV2A modulators or slow sodium channel inhibition could optimize the seizure control following VNS. However, these data should be replicated in further randomized controlled studies.

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Candidates for epicranial focal cortex stimulation in an outpatient cohort of an epilepsy reference center

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Purpose: Epicranial focal cortex stimulation (FCS) in epilepsy is a new treatment option for patients with neocortical epilepsy. By stimulating via a pseudo-Laplace electrode arrangement minimally invasive long-term brain stimulation with alternating and direct current can be used to modulate cortical excitability. Experiences from the screening process in an unselected patient collective at an outpatient clinic from a tertiary epilepsy centre for a clinical trial are used to estimate the potential for clinical application of FCS.
Method: All patients in the outpatient clinic at the epilepsy centre in Freiburg seen between the 1st October 2019 and the 31st January 2020 were screened for eligibility for a clinical trial (PIMIDES: patient-individualised modulation and intervention through epicranial stimulation). Criteria relevant for clinical application and trial-specific in- and exclusion criteria were separately analysed to identify typical patient characteristics determining FCS candidates' eligibility.
Results: 562 epilepsy patients were screened. In 205 (36.5%) of patients the underlying epilepsy syndrome precluded FCS (generalised epilepsies 11.6%; mesiotemporal 17.6%; unclassified 7.3%).

222 (39.5%) patients had a neocortical lesion, and in 35 out of 135 patients with focal nonlesional epilepsy a necortical focus was determined based on EEG and/ or semiology.
Of these 257 patients with a focus potentially accessible to FCS 95 had established pharmacoresistance, thus were in need for non-medical treatment options. Overall, to 16.9% of all epilepsy patients FCS could be potentially offered as a treatment option. Only 10/257 patients, however, fulfilled all inclusion criteria for the clinical study.
Conclusion: A relevant proportion of patients consulting a tertiary epilepsy centre has a neocortical focus. These patients are thus potential candidates for FCS when drug resistance is established. Inclusion and exclusion criteria for clinical studies are highly selective and do not reflect the potential clinical use.

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Impact of VNS therapy on quality of life and cognitive function in the treatment of drug-resistant epilepsy

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Purpose: The purpose of the treatment of drug-resistant epilepsy (DRE) is to control seizures but also to improve quality of life (QoL) and reduce adverse effects of medications to improve compliance with drug therapy. This pilot study aims to explore the efficacy of VNS on QoL and cognitive performance in patients suffering from DRE referred to the Epilepsy Center of the University Polyclinic of Monserrato, Cagliari, Italy.
Method: Thirty-one subjects with DRE who were not candidates for surgical therapy were selected. The frequency, type, and intensity of seizures were recorded during the observation period (≥12 Months).
Patients were assessed by EPI-QoL questionnaires and neuropsychological tests. The Wilcoxon test was used to compare the questionnaires before and after VNS. Spearman's correlation was used to analyze the correlation between increased QoL and reduced seizures.
Results: QoL and MMSE show a significant increase after VNS (p= 0 0004 e p= 0 0282, respectively), with no significant correlation with seizure improvement (Spearman's correlation p= 0 7940 and p= 0 8995).
Conclusion: Despite the small sample size, this pilot study shows a benefit of VNS on QoL independent from seizure control that would also tend to maintain and improve mood and cognitive deficits over time. Of course, further studies will be needed to clarify how VNS modifies the neuronal network in DRE patients in order to exert an antiepileptic and beneficial effect on cognitive processes.

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The correlation between preoperative sleep stage and seizure outcome in adolescents and adults undergoing vagus nerve stimulation

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Purpose: The vagus nerve stimulation (VNS) has been reported to exert an effect on the sleep cycle, and its treatment response is correlated with the connectivity of thalamocortical tracts. We examined the correlation between preoperative sleep stage and seizure outcome follow-

ing VNS.
Method: We evaluated the correlation between sleep stages on the first day of long-term video-EEG monitoring and postoperative seizure outcome after VNS in patients aged 18 years or older at the time of surgery.
Results: The study population consisted of 19 patients (14 men, 5 women) with a mean age of 36 years (range 18-74). The seizure types were focal to bilateral tonic-clonic seizures in 12 patients, focal aware seizures in 2, focal impaired awareness seizures in 2, and generalized onset seizures in 3. At 2 years after surgery, the seizure outcome was classified as 1 case of class I, 8 of class II, 5 of class III, and 5 of class V according to the McHugh classification. In the 11 patients with sleep stage N2 or greater with clear sleep spindles, the seizure outcome was also class I in 1 patient, II in 8 patients, and III and V in 1 patient each, with class I and II accounting for 82% of the seizure outcome. Of the remaining 8 patients without clear sleep spindles, 2 showed low amplitude EEG, 4 had indistinct spindle-like waves, 2 had sustained slow waves from awake period. Seizure outcome in these 8 patients was classified as class III and V.
Conclusion: Our findings suggest that postoperative outcome of VNS is favorable for patients with confirmed sleep stage N2 or greater at the preoperative examination, despite the limited observation period of sleep.

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Emergency department (ED) visits and hospitalizations following neurostimulation for drug-resistant epilepsy (DRE)

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Purpose: Between 30-40% of adults with epilepsy do not respond adequately to anti-seizure medications. Patients with drug-resistant epilepsy (DRE) have poorer quality of life and incur almost twofold higher mean annual healthcare costs. While all have shown efficacy in DRE, there is a lack of comparative effectiveness data.
Method: A US healthcare claims database was utilized to identify DRE patients who underwent VNS, RNS, DBS (2012-2019). The index date was the earliest date on which a procedure was identified. Patients were allocated into two cohorts (VNS, RNS/DBS) and were propensity matched for the 2 years prior. Kaplan-Meier methods and log-rank tests were used to contrast the incidence of ED visits and HOSP during the 24-month follow-up period; corresponding rates were reported per 100 person-months (PMs) and compared using Poisson regression. All-cause and epilepsy-related healthcare utilization were assessed.
Results: 179 VNS patients met the selection criteria and were equally matched to RNS/DBS patients. VNS patients were less likely to experience the composite outcome (HOSP/ED visit) during follow-up on both an all-cause (55.9% vs. 96.6%) and epilepsy-related (49.2% vs.

95.0%) basis (both p<0.001). Rates of the composite outcome were numerically lower for VNS patients, albeit not significantly, 14.5 per 100 PMs vs. 18.2 per 100 PMs [epilepsy-related, p=0.134]), and the median time to the composite outcome was 12.6 months for VNS vs 8.3 months for RNS/DBS (p=0.0328).
Conclusion: Use of VNS was associated with significantly lower proportions of patients with all-cause and epilepsy-related ED visits and/or HOSP compared to RNS/DBS over the 24-month period following implantation. Results were largely attributable to differences in HOSP. Further research is needed to understand how reduced utilization of these services is associated with other health benefits.

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Vagal nerve stimulation in developmental encephalopathies and epilepsy: a narrative review

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Purpose: In pediatrics, developmental encephalopathies and epilepsy (DEE) play an important role in the group of drug-resistant epilepsies, because associated with the multiple comorbidities that they generate, they cause important psychosocial alteration in our patients; That is why in the last decade the use of vagus nerve stimulation (VNS) as adjuvant therapy for seizure control has been implemented. In the next article, we collect evidence on the effectiveness of the use of VNS as adjuvant therapy in developmental encephalopathies and epilepsy
Method: PUBMED, EMBASE, and Cochrane databases were searched through April 2022 for original articles on VNS in developmental encephalopathies and epilepsy, without restriction on language or year of publication, including a total of 25 articles. all retrospective, which included the following pathologies: CDKL5, Rett, tuberous sclerosis, progressive myoclonic epilepsies, non-ketotic hyperglycinemia, Berardinelli-Seip syndrome, Gaucher III and Unverricht Lundborg.
Results: In the 25 articles, a total of 116 patients were found, of which 14% presented an improvement of the crises between 80-100%, 59 % between 50-79%, and 20% less than 50%. and only 7% showed no improvement. Additionally, additional benefits of improvement in other aspects such as behavior, alertness, concentration, quality of life, and communication skills were evidenced.
Conclusion: Of the total 116 patients, seizure control of more than 50% was reported in 73% of them, jointly evidencing improvements in terms of alertness, behavior, and neurodevelopment, which may favor the approach of this therapy. a possibility of non-pharmacological and palliative management. Prospective studies are required to evaluate not only the reduction in crisis frequency but also these other qualities of life parameters.

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Effectiveness of continuous theta burst transcranial magnetic stimulation targeting cerebellar dentate nucleus in patients with drug-resistant epilepsy: a randomised, controlled, double-blind, crossover clinical trial

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Purpose: Transcranial magnetic stimulation (TMS) has emerged as the most promising non-invasive therapy for patients with drug-resistant epilepsy (DRE) not suitable for surgery, but its optimal stimulation target and paradigm remain inconclusive. In this study, we aimed to investigate the effectiveness of neuronavigation-guided continuous theta burst stimulation (cTBS) targeting the cerebellar dentate nucleus (CDN) for the treatment of DRE.
Method: This study was a single-centre, double-blind, randomised, sham-controlled, crossover clinical trial. Patients with DRE ≥ two years and seizure frequency ≥ two seizures every month were enrolled from August 2, 2021 to February 6, 2022 at Xijing Hospital, China. Patients were 1:1 randomised to receive active CDN-cTBS followed by sham stimulation or vice versa. All patients and investigators except the TMS deliverer were blinded to allocation. Bilateral CDNs were alternately targeted by cTBS (intensity at 80% resting motor threshold, 1200 stimuli at each CDN) which was navigated by three-dimension reconstruction of MRI, once daily on workdays for two weeks. Primary outcomes were the percentage of seizure frequency reduction and the response rate in the per-protocol population within two months after treatments as compared with baseline. This trial was registered at ClinicalTrials.gov (NCT05042726).
Results: 44 patients were randomised and 38 patients (18 [47%] female; median age, 31 [24-40] years) were included in the final analysis (18 in the active stimulation-first group, 20 in the sham stimulation-first group). CDN-cTBS significantly increased the percentage of seizure frequency reduction as compared with sham stimulation (difference between treatments [95% CI]: 25% [5%-46%], adjusted p = 0.018). The response rate after CDN-cTBS treatment was significantly higher than sham stimulation (difference between treatments [95% CI]: 24% [11%-40%], adjusted p = 0.029). Few adverse events (5.26% moderate headache, 2.63% tinnitus, 2.63% dizziness) were reported during active stimulation, which resolved spontaneously after stimulation.
Conclusion: Neuronavigation-guided CDN-cTBS was an effective and well-tolerated TMS strategy for DRE.

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The impact of cortical stimulation on the surgical decision depending on electrographic patterns

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Purpose: Cortical stimulation (CS) is increasingly used for functional mapping and seizure onset zone (SOZ) localization; however, it is not a routine practice in all comprehensive epilepsy centers. The purpose of the study is to evaluate the impact of performing CS for mapping and seizure onset zone localization as part of the presurgical evaluation in patients with drug resistant epilepsy (DRE) implanted with depth electrodes (DE).
Method: Patients with DRE who were admitted to our Epilepsy Monitoring Unit with DE from October 2018-December 2022 and underwent CS for surgical planning, were included in the study. Demographic data was collected, as well as history of epilepsy, presurgical investigations, results from DE evaluation, CS (time, frequency, location, duration, after discharges (ADs)), surgical decision, and outcomes after epilepsy surgery.
Results: 101 patients were implanted with DE, and of the 44 that were analyzed, 33 met inclusion criteria. Mean age at implantation was 35 years (19-64 years; SD12), 52% were female(n=23). 22.7% patients(n=10) had their typical seizure during CS. The most frequent reason for SEEG implantation was having lesional epilepsy (n=12, 27.3%) followed by suspicion of more than one foci (n=10, 22.7%). Epilepsy surgery was recommended for 34% of patients included in the study (n= 15). The hypothesis of the epileptogenic zone was correct in 65.9% (n=29) of cases. After discharges did not change the decision for surgery or the final hypothesis ($p>0.05$). The preferred duration of pulse stimulation was 5 seconds in 56.8% (n=25) and the median CS duration was 90 minutes (10-240min, SD 60). The resection area changed in 29.5% (n=13) of cases after CS was concluded, when compared to initial SOZ hypothesis.
Conclusion: CS may have an impact on surgical decisions and outcomes of patients with DE implantation and should be encouraged as a part of presurgical planning in all cases.

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Music in brain - intracerebral study in patients with epilepsy

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Purpose: The effects of music on epileptic brain activity were measured by intracerebral electrodes (SEEG) implanted in the brains of 18 epilepsy patients prior to surgery.
Method: Listening to Mozart led to a 32% decrease in epileptic discharges (ED), listening to

Haydn's Surprise Symphony No 94 caused a 45% ED increase.
Men and women responded differently. Listening to Haydn's music led to suppressed ED only in women; in the men, there was an increase of ED discharges. The acoustic analysis revealed that non-dissonant music with a harmonic spectrum and decreasing tempo with significant high-frequency parts has a reducing effect on interictal ED in men. To reduce ED in women, the music should additionally be, in terms of loudness, gradually less dynamic.
In the SEEG ongoing study in 23 patients Mozart Piano Concerto 27 had the best effect, however antiepileptic effect was observed also while listening to Saint-Saens and Phillipe Glass music. The relaxation music often aggravated ED. According to subjective rating made by the patients EDs reducing compositions were considered as rather unpleasant for listening.
Results: The acoustic analysis revealed that non-dissonant music with a harmonic spectrum and decreasing tempo with significant high-frequency parts has a reducing effect on interictal ED in men. To reduce ED in women, the music should additionally be, in terms of loudness, gradually less dynamic.
Conclusion: The 'Mozart effect' in epilepsy was confirmed. The acoustic characteristics of music are responsible for suppressing brain ED. The use of musical pieces with well-defined acoustic properties are important for studying individual impact of music in patients with epilepsy. Music exposure is a potential method of non-invasive therapy in patients with epilepsy.

Mozart effect in epilepsy: Why is Mozart better than Haydn? Acoustic qualities-based analysis of stereoelectroencephalography. Stillova, K ...Strycek, O... Rektor, I. EUROPEAN JOURNAL OF NEUROLOGY, 2021, 28: 5, 1463-1469

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Circadian-related cortical dynamics in juvenile myoclonic epilepsy (JME) using transcranial magnetic stimulation coupled with electroencephalography (TMS-EEG)

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Purpose: Cortical excitability indexes have been shown to increase with time awake amongst healthy individuals. People with juvenile myoclonic epilepsy (JME) show increased incidence of seizures and longer interictal epileptiform discharges (IEDs) upon awakening and may therefore have abnormal circadian cortical excitability dynamics.

We investigated whether circadian-related cortical excitability and corticothalamic indexes differed between JME patients and controls using transcranial magnetic stimulation coupled with EEG (TMS-EEG). We also tested whether differences in these indexes 1) reflected changes in IED characteristics and 2) could estimate recent seizure activity.

Method: TMS-EEG data were obtained from 9 JME patients and 7 healthy controls in a morning (AM) and afternoon (PM) session. Immediate response slope (IRS) and the most powerfully evoked frequency (i.e., natural frequency, NF) of each TEP were used to index cortical excitability and corticothalamic oscillatory activity, respectively. IED duration and frequency were obtained using 24-hour ambulatory EEG recordings. Recent seizure activity was defined as the occurrence of the most recent generalised tonic-clonic seizure. Changes in TMS-EEG indexes from AM-PM were compared within and between groups. Associations between TMS-EEG indexes and IED characteristics or seizure activity were investigated using regression analyses.
Results: In controls, IRS increased (p=0.04) and NFs decreased (p=0.05) from AM to PM. AM-PM changes in JME patients were less consistent. NF values were slower in the JME group when accounting for the effect of AM vs PM session (Skillings-Mack test: p=<0.01). IRS and NF changes were not predicted by IED characteristics in a linear regression analysis. AM-PM NF difference was the only significant predictor of the time from the last generalised seizure in a linear regression model.
Conclusion: We confirmed that cortical excitability increases from AM-PM in healthy subjects. In JME patients, we observed distinct NF values and dynamics which were not associated with IED activity but possibly linked to seizure control.

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Vagus nerve stimulation in elderly with epilepsy

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Purpose: Vagus nerve stimulation (VNS) is a non-pharmological intervention in refractory epilepsies which stands out not only as a promising therapeutic strategy in reducing seizure frequency, but also the polypharmacy in the elderly and thereby preventing drug interactions, managing frailty and assuring a higher adherence to antiseizure medication (ASM). The objective was to compare the efficacy of VNS in elderly in comparison to younger patients.
Method: All participants were patients with refractory epilepsy who were treated with VNS. They were followed up during 3 years after the implantation. Patients aged ≥60 years were compared to patients aged <60 years. The outcome parameters were responder rate, defined as ≥50% reduction in seizures per month, and seizure freedom.
Results: We included a total of 144 patients wir refractory epilepsy (32 over 60 years of age). The age-stratified average age at the time of VNS Implantation was 32.6 ±11.1 vs. 65.4 ±4.9 years. The overwhelming majority of the participants suffered from a focal epilepy. After 3 years follow up, seizure freedom could be achieved in 13.4% of the patients aged <60 years, in comparison, to a seizure freedom of 10.6% in patients aged ≥60 years.. It could be shown that the therapeutic effects were slightly better in the group of younger patients with a longitudinal increase in the responder rate, whereas the elderly patients did not show a statistically significant improvement beyond two years.

Conclusion: The younger epilepsy patients seem to have a higher chance of seizure freedom if treated by VNS. The ceiling effects in response to the therapy, which was reached after 2 years in elderly population, might be caused by a worse synaptic plasticity in advanced age. Apparently, the indication for VNS should be estimated early in the course of the disease in order to improve the efficacy.

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Real-world data on deep brain stimulation of the anterior nucleus of the thalamus for drug-resistant epilepsy using a continuous stimulation setting

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Purpose: We aimed to evaluate the outcomes of patients with drug-resistant focal epilepsy treated with deep brain stimulation targeting the anterior nucleus of the thalamus (ANT-DBS) using a continuous stimulation, as opposed to the conventional cyclic stimulation setting.
Method: We conducted a retrospective analysis of the clinical data and stimulation parameters of eight patients with drug-resistant focal epilepsy and bilateral ANT-DBS implantation in our center. A protocol of continuous stimulation was used for all patients. Modality (monopolar n=7, bipolar n=1) and averages of frequency 150Hz (130-170), amplitude 5.2 V (4 –6.1) and pulse width 105ms (90-120) were individually tailored to maximise clinical benefit.
Results: At the time of DBS intervention, the mean age and epilepsy duration were 39 years and 19 years, respectively. All patients had frequent seizures (≥3 per week). Reported etiologies were focal cortical dysplasia type 1 (n=1), autoimmune encephalitis associated with GAD antibodies (n=1), herpes virus simplex 1 encephalitis (n=1) and unknown (n=4). Once comprehensive presurgical evaluation was finished, resective surgery was not considered to be appropriated due to a multifocal onset of seizures (n=7) or overlap of the epileptogenic zone with eloquent cortex (n=1). After a mean follow-up period of 3.3 years (8 months-10 years), 75% of patients showed significant (>50%) seizure reduction, including two cases with >90% decrease in frequency. Overall number of antiseizure medications remained unchanged. None presented serious adverse effects. Depression was seen in two cases and worsening of apathy in one patient, being these numbers similar as in clinical trials.
Conclusion: In our cohort, neuromodulation therapy with ANT-DBS using continuous stimulation proved to be a safe and effective treatment for patients with drug-resistant focal epilepsy who are not candidates for surgical treatment.

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Vagus nerve stimulation in refractory epilepsy: a retrospective study in a reference centre

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Purpose: Vagus Nerve Stimulation (VNS) is an adjunctive therapy for patients with refractory epilepsy who are not candidates for surgical resection or had poor outcomes after surgery. Prognostic factors and established standards for outcome measurement after VNS implantation are still lacking. Characterize the population, describe the outcomes and identify potential prognostic factors of the epileptic patients submitted to VNS in our center.
Method: Retrospective study, including consecutive adult and pediatric patients treated with VNS between 2013 and 2022 with a minimum 1 year follow-up. VNS response was evaluated using McHugh classification and patients were divided into two groups – responder group (>50% reduction in seizures frequency) and non-responder group (<50% reduction in seizure frequency). Eight clinical factors (age at onset; age at implantation; gender; epilepsy duration; brain surgery background; type of seizure; brain MRI finding and follow-up time) were analyzed among both groups.
Results: During this period 35 patients were implanted with VNS, mean age 26.06 ± 13.94 years. After an average follow up of 4.66 ± 2.13, 57.14% were responders (McHugh class I 17.23%, class II 39.91%) and 42.86% non-responders (McHugh class III 22.86%, class IV 2.86%, class V 17.14%). In both groups, female patients were dominant, the majority had no previous brain surgery and a positive MRI. Statistical analysis found an association between a younger onset age and response to VNS procedure (univariate analysis $p = 0.008$; multivariate analysis $p = 0.009$), and also with multifocal seizures (univariate analysis $p = 0.015$; multivariate analysis $p = 0.004$).
Conclusion: Our series had similar outcomes to previous published series. We found that multifocal seizures and younger age at seizure onset were associated with a better response, acting as potential positive predictors of VNS outcome. Further investigation is required to to accurately predict and improve the outcome after VNS implantation.

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Responsive neurostimulation (RNS) is associated with significant seizure reduction in occipital epilepsy: analysis of 2 cases

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Purpose: There are relatively few if any reports regarding the outcome of patients with occipital epilepsy treated with RNS and this report seeks to characterize the clinical course of 2

such patients who had significant seizure reduction over time after RNS placement.
Method: A retrospective qualitative review of 2 clinical cases is presented and clinicopathologic features and quantitative RNS datasets are analyzed for review
Results: Significant and incremental seizure reduction may occur over time post RNS placement even with relatively low amounts of cortical stimulation, and this report will review these cases.
Conclusion: RNS significantly reduced seizure activity in occipital epilepsy cases that were not candidates for resection in this small case series.

Nursing

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Implementation of a clinical care pathway for patients with refractory epilepsy for evaluation for epilepsy surgery and other specialist treatments in a regional epilepsy centre

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Purpose: To improve and enhance the specialist care provided to patients with refractory epilepsy and to improve access to epilepsy surgery program and other specialist treatments such as ketogenic diet and immunotherapy in a systematic and streamlined approach in the regional Epilepsy service at St. James' Hospital, Dublin.
Method: Based on clinical experience of managing patients with drug resistant epilepsy we identified a quality gap in referral for surgery workup causing delays and under-referral for surgical evaluation and deficiency in communication with our surgical centre. To improve this quality gap our service developed an ANP led clinic specifically for diagnostic and pre-surgical evaluation as well as evaluation other treatments such as ketogenic diet and immunotherapy. This includes a structured follow-up structure until after the surgery is completed
Results: Since the development and implementation of a Clinical Care Pathway for Patients with Refractory Epilepsy and Advanced Nurse Practitioner-led refractory clinic in 2020/2021 at St. James' Hospital Dublin, 47 patients with refractory epilepsy have been referred to our national tertiary centre for vEEG monitoring, 26 patient cases have been presented at Epilepsy Surgical Review Meeting (ESRM) and 10 epilepsy surgeries have been completed during this period. We have had very positive responses from patients who have gone through this pathway.
Conclusion: Through the development and implementation of this pathway, patients with drug resistant epilepsy are being identified and referred for further evaluation in a more efficient and timely manner. These patients receive specialist review and support during their journey on the Clinical Care pathway. Advanced Nurse Practitioners in Epilepsy are well positioned to manage and advocate this complex patient cohort on this pathway.

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Approaches of emergency nurses to pediatric epileptic seizures in turkey: a cross-sectional, multicenter study

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Purpose: It is important to determine the approaches of emergency departments (EDs) nurses to seizures in order to prevent mortality and morbidity resulting from active seizures. The purpose of this study is to determine the approach of EDs nurses to children with epileptic seizures in Turkey.
Method: This cross-sectional, multicenter on-line survey study design was conducted among 162 nurses working in an EDs setting in Turkey between 2nd August and 1st December 2022. The data-collection form was developed by the research team in line with the literature to evaluate the interventions of nurses working in different EDs of Turkey to children with epileptic seizures. This form consisted of two sections. The first section of the form is to determine the characteristics of the nurses and characteristics of EDs (four items). The second section of the form included a case report of a child who had an epileptic seizure. Numbers, percentages, means, and standard deviations were used for data analysis.
Results: The most difficulty issues of the the nurses to attempt in a child with epileptic seizure were to help calm a parent, to attempt IV access, and to determine the type of seizure. About half of the nurses correctly defined the epileptic seizure type in the case report. The nurses responded to the medical therapy they applied in the EDs, according to the phases of seizure intervention. According to the responses; in the first-line therapy; rectal diazepam was applied after that IM midazolam, IV diazepam, and IV midazolam were applied. In the second-line therapy; IV diazepam was applied after that IM midazolam, IV phenobarbital, and rectal diazepam were applied.
Conclusion: As a result of this study, while some of the practices for the management of epileptic seizures are correct, there are also some wrong interventions of the nurses.

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The virtual epilepsy specialist nurse in prison – a service evaluation project

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Purpose: Many services needed to change the way health care was delivered due to the pandemic, this included the prison epilepsy clinic led by the epilepsy specialist nursing team. A service evaluation of the virtual service compared to a face to face clinic held in the prison's healthcare suite was carried out between 2020 -2023. Cardiff prison has capacity for up to 820 men aged 18 and above. People with epilepsy should have access to specialist care and

support (NICE 2019, Welsh Government 2019). Quality statements support the well-being of prisoners and ensure safe and effective care (NICE 2017).
Providing healthcare to people in prison has challenges and this was highlighted more so during the height of the pandemic. The prevalence of seizures and epilepsy in prison is four times higher than the general population, with lower engagement in healthcare (Marshall et al. 2001, Birmingham 2003). It is evident the prison patient population are one of the most vulnerable groups regarding healthcare.
Method: A retrospective evaluation of initial referral to time of review for face to face and virtual clinics and a retrospective review of attendance to the face to face and virtual clinic between 2020 -2023. Written feedback from prison officers, prison healthcare staff on the virtual clinic and use of the resources and feedback from the men using the clinic.
Results: Reduced waiting list times 9-42 days from referral to review by epilepsy specialist nurse compared to 3-6 months when the clinic was conducted in the prison.
Improved attendance rate with the virtual clinic from 50% to 80%
Positive feedback from healthcare staff and patients with a request to continue the virtual service despite the lifting and easing of restrictions.
Conclusion: Improved access to epilepsy specialist service. Reduced waiting times. Improved attendance rate. Efficient use of resources.

Paediatric Epileptology

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Comparison of clinical, electroentephalographic and tomographic data in children with controlled and non-controlled epilepsy

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Purpose: To analyze importance of etiology of neonatal seizures in formation of epilepsy in children of early age.
Method: There were 236 children at the age of 3 who suffered neonatal seizures under supervision. All patients underwent somatic and neurological examination, EEG, EEG video monitoring, MRI of the brain, laboratory methods with metabolic control, genetic testing and virological examination in the neonatal period and later
Results: During the survey etiological factors of neonatal seizures were determined: hypoxic-ischemic encephalopathy (47%), intracranial hemorrhage and vascular diseases (11%), prenatal infections (7%), postnatal neuroinfections (3%), metabolic electrolyte disorders (4%), developmental disorders (dysgenesis) (8%), facomatosis (2%), withdrawal syndrome (1%), congenital metabolic desorders (2%), chromosomal syndromes (1%), congenital tumors (1%), benign neonatal seizures (3%), somatic diseases (1%), postnatal trauma (1%), not specified (8%). According to the classification of etiology of epilepsy (32nd International Congress on Epilepsy, 2017) all patients were distributed as follows: structural -67%, genetic - 4%, infec-

tious - 10%, metabolic - 4%, immunological - 1%, not specified - 8%, mixed - 6%.
According to outcomes regarding the formation of epilepsy and neurological deficiency all children at the age of 3 were divided into 3 groups: (1) without seizures up to 3 years of age and without formation of a neurological deficiency (61%); (2) with formation of epilepsy, in which medication remission was achieved, and moderate neurological deficiency (16%); (3) with formation of drug-resistant epilepsy and severe neurological deficiency (23%).
Conclusion: patients in the 1st group had neonatal seizures due to light hypoxic-ischemic encephalopathy, somatic diseases and transient metabolic disorders. In the 2nd group causes of neonatal seizures and further epilepsy were moderate hypoxic-ischemic encephalopathy, postnatal neuroinfections and postnatal trauma. Patients with formation of drug-resistant epilepsy more often had severe hypoxic-ischemic encephalopathy, intracranial hemorrhage, congenital malformations, prenatal infections, congenital metabolic disorders, developmental disorders

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The new ILAE definition of Lennox-Gastaut syndrome: practical implications and limitations

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Purpose: There are three major changes in the new definition of Lennox-Gastaut syndrome (LGS) compared with the traditional definition: (1) onset prior to 18 years, (2) must include tonic seizure, (3) generalized slow spike-waves (SSW) and (instead of or) generalized paroxysmal fast activity (GPFA) on electroencephalography (EEG). We investigated the practical implications and potential limitations of the new LGS definition based on a large cohort of patients in an exploratory study.
Method: This was a retrospective database study. All patients with an electro-clinical diagnosis of LGS (based on its traditional definition) at the outpatient epilepsy clinic at Shiraz University of Medical Sciences, Shiraz, Iran were included (from 2008 until 2020). Patients were reclassified based on the new definition of LGS.
Results: In total, 3737 patients were registered. Based on its traditional definition, 300 patients were diagnosed as having LGS. According to the new definition of LGS, only 96 patients (32% of the traditional cohort) had LGS. One patient had an age at onset of 21 years; 29 patients (9.7%) did not have SSW in their EEGs; 139 people (46.3%) did not have GPFA in their EEGs; and, 111 patients (37%) did not report having tonic seizures.
Conclusion: The new ILAE definition of LGS has some important practical implications and limitations. Before reinforcing and making this new definition compulsory in future research and clinical practice, more work is needed to enlighten various aspects of such changes in the definition of this epilepsy syndrome.

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Serial electroencephalographic findings before the onset of juvenile myoclonic epilepsy: a case series

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Purpose: We aimed to delineate the clinical and electroencephalographic transition in patients with juvenile myoclonic epilepsy who were followed-up long-term before onset of juvenile myoclonic epilepsy.
Method: We enrolled juvenile myoclonic epilepsy patients whose course of epilepsy had been observed for more than five years before the onset of juvenile myoclonic epilepsy, those who had undergone electroencephalogram recording more than twice before the onset of juvenile myoclonic epilepsy, and those who had terminated antiseizure medications for at least two years before the onset of juvenile myoclonic epilepsy. Patients who had transitioned from childhood absence epilepsy to juvenile myoclonic epilepsy were excluded. We retrospectively reviewed the medical records and neurophysiological data of the patients.
Results: Four patients met the inclusion criteria. One patient was diagnosed with febrile seizures during childhood, and the remaining three had transitioned to juvenile myoclonic epilepsy from other epileptic disorders, such as self-limited epilepsy with autonomic seizures, genetic epilepsy with febrile seizure plus, or non-specific genetic generalized epilepsy.All had generalized spike-wave discharges or photoparoxysmal responses for more than two years before onset of juvenile myoclonic epilepsy.
Conclusion: Generalized spike-waves on electroencephalogram during the course of any type of epilepsy or febrile seizure may be a risk factor for developing juvenile myoclonic epilepsy. When generalized spike-waves are present during childhood in individuals with febrile seizures or pediatric epilepsy, follow-up examinations and careful clinical interviews are crucial.

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Efficacy of steroids in seizure control and dipole stabilisation in drug resistant electrical status epilepticus in sleep due to structural cause

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Purpose: To devise objective measures to evaluate the role of steroids on dipole stabilisation and seizure control in Electrical Status Epilepticus in Sleep due to structural causes.
Method: 20 children aged 2-12 years with drug resistant epilepsy and ESES with Spike-wave index>50% and structural lesions in MRI included.EEG assessment done at 0,3,6 months and one year of starting therapy.SWI and Stability quotient(SQ) calculated at each EEG assess-

ment.Using a source localisation software,the spikes were averaged by automated pattern matching with a similarity threshold of 60%.Stability quotient =Total number of Averages÷N. Intravenous Methylprednisolone pulse therapy given at 30mg/kg/day for three consecutive days for six months.Seizure control defined as atleast 50% reduction in seizure frequency. Dipole stabilisation defined when both Stability-quotient ≥ 0.8 and Spike-wave index< 50%.
Results: 18 children (90%)had seizure control at 6 months of starting steroid pulse and 15 of 20 children (75%)maintained this at 12 months.18 children had stability quotient of <0.8 before starting pulse and 14 (77.78 %)on follow up improved their stability quotient to ≥ 0.8 at 6 months and 12(66.67%) maintained this at 12 months.15 children(75%)had SWI <50% at 6 months and 13(65%) at 12 months. Statistical association between seizure control and SWI and SQ together and SWI alone not statistically significant at 6 months but significant at 12 months.Statistical association between seizure control and SQ alone was statistically significant both at 6 months and 12 months.SQ alone at 6 months have statistically significant association with seizure control at 12 months.
Conclusion: Steroids helps in clinical and EEG dipole stabilization.Thus steroids can serve as an effective bridging therapy and its efficient but temporary stabilizing effect on lesional cases of ESES ought to give valuable time when appropriate investigations can be planned for invasive or non invasive procedures.Assessing SQ along with SWI as a measure of dipole stability gives better association with seizure control.

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Myoclonic status epilepticus is associated with unfavorable outcomes after pediatric cardiac arrest

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Purpose: Myoclonic status epilepticus (MSE) after cardiac arrest (CA) is usually associated with unfavorable outcome in adults, but limited data are available among children. We aimed to evaluate the association of MSE with outcomes after pediatric CA.
Method: This was a retrospective single-center cohort study of pediatric CA from 2005-2019. EEG initiated within 24 hours of CA was reviewed for MSE and background, classified as normal, slow/disorganized, discontinuous/burst-suppression, or attenuated/featureless. CA factors were collected from the medical record, including witnessed-monitored status, number of epinephrine doses, and post-CA lactate. Outcomes were unfavorable (Pediatric Cerebral Performance Category [PCPC] change ≥1 from baseline resulting in hospital discharge score ≥3) and in-hospital death. Multivariable logistic regression assessed associations of MSE with outcomes. Fisher's exact test assessed association of EEG background with death among pa-

tients with MSE.
Results: We analyzed 141 children (median age 2.9 (IQR 0.7-9.7) years). Thirty-eight (27%) children had seizures, including 29 (21%) with SE. Thirteen (9%) had MSE. CA was witnessed-monitored for 83 (60%), patients received a median of 1 (0-3) epinephrine dose, and median post-arrest lactate was 3.7 (2.1-7.1). EEG background was normal in 23 (16%), slow/disorganized in 73 (52%), discontinuous/burst-suppression in 21 (15%), and attenuated/featureless in 24 (17%). Unfavorable outcome occurred in 87 (62%), including 35 (25%) who died. All children with MSE had unfavorable outcome, including 7 (54%) who died. After controlling for witnessed-monitored status, epinephrine doses, and post-CA lactate, MSE was not significantly associated with death (OR=3.06, 95%-CI 0.71-13.1, P=0.13). EEG background was associated with death among those with MSE (χ^2=7.6, P=0.01).
Conclusion: All children with MSE after CA had unfavorable outcome at hospital discharge. While MSE was not independently associated with increased risk of death, those who survived had severe disability or were in a coma/vegetative state. Among children with MSE, EEG background was associated with death.

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Epileptic seizures – possible manifestation of SARS-CoV-2 infection in children

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Purpose: The aim of this study is to evaluate the incidence of epileptic seizures in children who have been diagnosed with COVID-19, as well as the patients' evolution and prognosis.
Method: Our study group consists of 25 children aged 21 days-17 years, who were evaluated between March 2020-March 2022 in the Department of Pediatric Neurology in our hospital and who tested positive for SARS-CoV-2. From these patients, 7 had previously been diagnosed with epilepsy. Computered tomography scans were performed for the patients who presented epileptic seizures for the first time in the context of COVID-19. Due to the viral infection, electroencephalograms could not be recorded. All patients underwent electroencephalography after one month since the hospitalization.
Results: Among the patients who had previously been diagnosed with epilepsy, 2 presented reoccurrence of seizures after a period of control under antiepileptic medication, the frequency of seizures increased in 4 cases, and one patient presented epileptic status. From the patients whose medical history did not reveal epileptic seizures, but manifested them in the context of SARS-CoV-2 infection, 2 presented febrile status epilepticus, 4 manifested febrile seizures, 2 presented more than two seizures, and the paroxysmal episode was singular in 10 patients. The epileptic seizures were the only manifestations of the SARS-CoV-2 infection in 18 patients. CT scans revealed 3 cases of cerebral edema. Electroencephalography recorded significant modifications in 13 patients, 7 of whom had previously been diagnosed with epilepsy. The outcome was favorable for all patients. Among the patients whose epileptic seizures onset occurred secondary to COVID-19, only those who presented recurrent seizures

received chronical antiepileptic treatment.
Conclusion: Seizures can be a part of the clinical presentation of SARS-CoV-2 infection in children, and in some cases these can be the very first or the only manifestation of the viral infection.

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Developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep in Saudi Arabia: electroclinical, etiologic, genetic, and outcome multicenter study

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Purpose: To investigate the clinical features of developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep (D/EE-SWAS), its electrographic characteristics, and etiology and to compare the effects of different treatment strategies on the outcomes using a Saudi Arabian database.
Method: This multicenter study included children with D/EE-SWAS who were evaluated between 2010 and 2020 at 11 tertiary centers. Data were collected on their baseline clinical features, etiologies, and treatment modalities. Seizure reduction, spike-wave index, and cognitive state were examined as potential therapeutic outcomes.
Results: Ninety-one children were diagnosed with D/EE-SWAS, with a median age of 7 years (IQR: 3–5) and an almost equal sex distribution. The average age at which epilepsy was diagnosed was 3 years (IQR: 5–2). A genetic/metabolic etiology was found in 35.1% of the patients, and a structural etiology was found in 27.4%. Children with underlying genetic/metabolic diseases exhibited an earlier seizure onset ($P = 0.001$) than children with other etiologies. Benzodiazepines (76.6%) were the most common treatment, followed by steroids (51.9%). Sodium valproate (75%) was the most frequently used antiseizure medication, followed by levetiracetam (64.9%). Children with a later seizure onset were more likely to have better clinical responses ($P = 0.046$), EEG responses ($P = 0.012$), and cognitive outcomes ($P = 0.006$) than children with an earlier onset. Moreover, better seizure response and electrographic response were seen in patients with bilateral interictal discharges on the EEG than otherwise. Children had a higher likelihood of both clinical and electrographic improvement with combination therapy of benzodiazepines ($P = 0.001$) and steroids ($P = 0.001$) than with other therapies.
Conclusion: This study shows a higher prevalence of genetic/metabolic causes and suggests the superior efficacy of combination therapy with steroids and benzodiazepines in D/EE-SWAS. Prospective studies that strictly assess the treatment protocols and outcomes are needed.

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Gas-chromatographic analysis of essential fatty acids (omega-3 and omega-6) in

venous blood of children with various forms of epilepsy

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Purpose: Omega-3 polyunsaturated fatty acids (n-3 PUFA) are believed to have neuroprotective effects, especially anticonvulsive effects (Ibrahim et al., 2018). Children with epilepsy might have lower n-3 PUFA levels than children without epilepsy, which was previously correlated to lower cognitive abilities (Bahgat et al., 2019). However, data is heterogeneous, depending on the gaschromatography protocol used, practiced nutrition and geographical region. The current literature is also heterogenous regarding the optimal ratio of omega-6 polyunsaturated fatty acids (n-6 PUFA) to n-3 PUFA-(n-6/n-3 ratio) for neurocognitive development (Yehuda et al., 2003). This pilot study analyzed baseline PUFA blood levels in children with epilepsy in a supraregional epilepsy center to establish a basis for further studies and to evaluate levels of n-3 PUFA in epileptic children together with nutrition and cognitive assessments.
Method: Children with heterogenous forms of epilepsy were recruited from the epilepsy center at University Hospital Ruppin-Brandenburg, Germany. EDTA blood was centrifugated and erythrocyte fraction was used for a fatty acid analysis via gas chromatography.
Results: Children with epilepsy (n=26) were in mean 11 years old (±4.6), significant differences in the n-6/n-3 ratio between girls (n=8) and boys (n=18) were found ($p<0.05$). The pediatric epilepsy patients had a mean n-6/n-3 ratio of 5.2 (±1.70). This exceeded the n-6/n-3 ratio of 4 that was proposed to be optimal for neurodevelopment before. Spearman correlation showed that n-3 PUFA and n-6 PUFA levels correlated negatively ($p<-0.35$).
Conclusion: This pilot study indicates that in a German paediatric epileptic population the n-6/n-3 ratio is higher than the ratio deemed necessary for an optimal neurocognitive development. It is now planned to include more patients in order to establish fatty acid reference values for children with epilepsy and to correlate fatty acid levels with cognitive assessments.

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Etiological and clinical spectrum of developmental and/or epileptic encephalopathy with spike-wave activation in sleep (D/EE-SWAS) – tertiary center experience in a cohort of 43 children

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Purpose: To evaluate the etiological and clinical spectrum of D/EE-SWAS, and to determine the most effective ASM.
Method: All patients with D/EE-SWAS treated from 2000-2022 were included. D/EE-SWAS was defined as epileptiform EEG activity >85% of slow-wave sleep associated with cognitive/behavioral regression. The investigated parameters were: the age of D/EE-SWAS and epilepsy onset; previous epilepsy and neurological/cognitive impairment; etiology; duration of D/EE-SWAS; EEG discharges; ASMs efficacy and outcome. The outcome at the end of the follow-up period was defined as favorable (D/EE-SWAS duration <2 years and reversion to previous neuropsychological state) and poor (D/EE-SWAS duration >2 years and/or neuropsychological regression). The ASM efficacy included electrical (>50% reduction of epileptiform EEG activity) and clinical responses. Descriptive statistics, Mann-Whitney U, and Kruskal-Wallis tests were used for statistical analysis.
Results: 43 patients with D/EE-SWAS were included. Etiology was: Self-Limited Focal Epilepsy of Childhood (SeLFE) in 20 (46.5%), structural brain abnormalities in 14 (32.6%), gene mutations in 7 (16.3%) (*GRIN2A, SETBP1, PAH, KIAA2022, COL4A1, COL4A2, TSC2*) and cryptogenic in 3 (7%) patients. Previous epilepsy was diagnosed in 37 (86%). The mean age of D/EE-SWAS onset was 70.1±30.5 (med 59, range 29-160) months. The mean duration was 28.9±27.2, (med 20, range 2-102) months. There is a statistically significant difference in D/EE-SWAS duration between the etiological groups (SeLFE, genetic, structural) (p=0.021) and between the patients with or without previous neurological/cognitive impairment (p=0.001). In children with SeLFE, the most effective ASMs were clobazam (64.3%), levetriracetam (44.4%), and corticosteroids (5/6), while in other etiologies sulthiam (50%), levetiracetam (44.4%), corticosteroids (41.7%) and clobazam (36.8%). Valproate is ineffective.
Conclusion: The etiology of D/EE-SWAS is heterogeneous. In most cases, it presents an evolution of SeLFE. The etiology and previous neurological/cognitive impairment had the highest impact on the outcome. The treatment is challenging and the most effective ASMs are clobazam, levetiracetam, corticosteroids, and sulthiame.

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≥75% and ≥80% responder rates reinforce the highly significant efficacy of stiripentol in Dravet syndrome patients - pooled analysis of the STICLO pivotal trials

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Purpose: This work reports efficacy results from the pooled analysis of data collected during the two placebo-controlled double-blind randomized trials of stiripentol in Dravet syndrome (STICLO France and STICLO Italy).
Method: Data from both STICLO pivotal trials were pooled and analysed in Intent-to-treat

Protocol. Different clinically relevant thresholds in seizure reduction in generalized tonic-clonic seizure (GTCS) frequency at two months of the double-blind period from 1m-baseline were defined: ≥50%, ≥75%, ≥80%, and seizure freedom (≥100%). STP efficacy was then evaluated by the percentage of patients achieving those thresholds, otherwise defined as 'responder rates'.
Results: Responder rates ≥75% and ≥80% were 54.5% and 51.5%, respectively, compared to 3.2% in the control group ($p<0.0001$ in both cases) on STICLOs pooled data analysis. Significant difference in efficacy was also observed for the ≥50% responder rate threshold with 69.7% for the STP *vs* 6.5% for the placebo group ($p<0.0001$). Also, while 36.4% of STP-treated patients were seizure free at 2m, none were in the control group ($p=0.0002$). Finally, STP administration led to a median decrease in GTCS frequency of 84.4%, compared to -5.8% in the placebo group.
Conclusion: Results of the pooled studies demonstrate the strong reduction in seizures frequency on STP and confirms the highly significant difference with the placebo-treated patients. Reducing frequency of GTCS may alleviate burden of the disease.

Acknowledgement: this study was supported by Biocodex.

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STP intrinsic anti-seizure activity: an update on its mechanisms of action

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Purpose: In 2007, stiripentol (STP) was granted its first marketing authorization as Diacomit® in Europe. At this time, STP was known as a positive modulator of GABA-A receptor (GABAA-R) mediated neurotransmission. Since then, several studies investigated and characterized STP biological properties.
Method: This work summarizes additional pharmacological activity of STP.
Results: STP is a positive allosteric modulator of GABAA-R with most efficient effect on GABAA-R containing α3 subunit. This selectivity may explain the clinical efficacy of STP in childhood-onset epilepsies, including Dravet syndrome (DS), as these subunits are highly expressed in immature brain.

STP activity is potentiated by benzodiazepines. Pharmacodynamic interaction studies suggest STP and benzodiazepines act independently on GABAA-R and polytherapy could increase the maximum effect beyond their respective activity used alone.

STP has also been found to inhibit lactate dehydrogenase thereby decreasing ATP production, limiting the inhibition of KATP channels which in turn diminishes neuronal excitability.
In neuronalglial cells exposed to oxygen-glucose deprivation, STP was neuroprotective when used prior the insult. In cells exposed to high glutamate levels STP at high concentrations was also neuroprotective. A significantly decreased cell injury after lithiumpilocarpine-induced

status epilepticus was also observed in hippocampus of young and adult rats.

Finally, recent data suggest STP could also interact with voltage-dependent calcium channels involved in abnormal thalamo-cortical oscillations underlying absence seizures. In particular, in vitro manual studies showed that STP inhibits T-type calcium and P/Q type channels.
Conclusion: STP is an antiepileptic drug harbouring multiple mechanisms of action. Its therapeutic efficacy observed in epilepsy derives from the sum of its biological properties and pharmacological actions rather than a single action. Further research is needed to better understand the relation between the different biological properties. and beneficial effects observed as well as characterize additional utility for other rare forms of epilepsy.

Acknowledgement: this work was supported by Biocodex.

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New aspects of clinical features and therapy in sunflower syndrome – a systematic review

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Purpose: Sunflower Syndrome (SFS) is a rare and poorly understood type of photosensitive epilepsy scarcely mentioned in the medical literature. Classic clinical findings include individuals looking towards the sun and waving a hand with abducted fingers in front of their eyes. This systematic review aimed to evaluate the current therapeutic approaches, psychosocial impact, and seizure characteristics to allow for a better diagnosis and therapeutic outcome in individuals with this rare phenomenon.
Method: A search of Embase, PubMed, Web of Science, and Scopus allowed for the identification and assessment of eligible studies. The SPIDER tool for qualitative evidence synthesis was selected to define the eligibility criteria; full-text screening was set based on the following criteria: Human studies, German, and English language, published after September 2019, and Individuals with SFS. PRISMA Guidelines for standardisation allow for a reproducible systematic review.
Results: 58 studies were reviewed, and 12 studies from western countries were analysed. This resulted in 142 eligible participants with SFS, out of which 75% were female. The age of onset of Handwaving Episodes (HWE) was at a mean age of 6.6±2.69 (SD) years. Characteristically, patterns of HWE and seizure exposure in natural light were seen among all patients. Ictal semiology was thought to be due to visual light exposure rather than HWE. Quality of life was mainly affected by SFS characteristics itself and not due to misdiagnosis (n=76). Combinational therapy of valproate and lenses resulted in seizure freedom in 14% out of 71 individuals having received pharmacological treatment. Fenfluramine seemed beneficial in the reduction of seizure frequency in 5.63% of individuals.

Conclusion: SFS remains a rare condition primarily affecting females. Seizures are challenging to treat. Combined approaches of valproates and lenses may result in the best management outcome. The role of fenfluramine needs further confirmation to be applied in medical practice.

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PRAX-562-101: a first-in-human phase 1 trial evaluating the safety, tolerability, pharmacokinetics and food effect of PRAX-562 in healthy volunteers

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Purpose: PRAX-562 is a next-generation sodium channel blocker in development for treatment of developmental and epileptic encephalopathies (DEE) with a unique biophysical profile that may translate to improved efficacy and tolerability over standard-of-care. We report findings from a first-in-human trial evaluating safety, tolerability, and pharmacokinetics (PK) of single and multiple ascending doses of PRAX-562, and the effect of food on PK of a single dose in healthy adults.
Method: PRAX-562-101 was a Phase 1 trial in healthy adults (18-55 years). Parts A (n=64) and B (n=32) were randomized, placebo-controlled and evaluated single (2.5-150mg) and multiple (30-120mg, 14 days QD) ascending oral doses of PRAX-562, respectively. Part C (n=16) was an open-label, randomized, crossover design evaluating PK of a single oral dose (90mg) in fasted and fed states. Part C participants were randomized to receive PRAX-562 in fed (following a high-fat/high-calorie meal) or fasted (≥10h after the last, and 4h before the next, meal) states.
Results: 112 participants were enrolled (n=88 PRAX-562, n=24 placebo). PRAX-562 was well-tolerated with no clinically significant safety findings in vital signs, laboratory results, physical exams, ECGs, or C-SSRS data; TEAEs were mostly mild (>92%).

Exposure increased dose proportionally over the evaluated dose range. PRAX-562 rapidly appeared in plasma with time to C_{max} between 2–3h, and detectable levels over a dose interval. 90mg in the fed state resulted in a slight C_{max} increase (9%), t_{max} delay (4 vs. 2.5h), and modest AUC increase (14%) vs. the fasted state.
Conclusion: PRAX-562 was well-tolerated in healthy adults at single doses up to 150mg (fasted) in Part A, at multiple doses up to 120mg QD for 14 days (fasted) in Part B, and at a single dose of 90mg in fed and fasted states in Part C. Our findings suggest PRAX-562 can be administered without regard for food.

Funding: Praxis Precision Medicines.

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PRAX-562-102: a phase 1 trial evaluating the safety, tolerability, pharmacokinetics

and pharmacodynamics of PRAX-562 in healthy volunteers

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Purpose: PRAX-562 is a next-generation sodium channel blocker with a unique biophysical profile that may translate to enhanced efficacy and a broader therapeutic window vs. current standard-of-care for developmental and epileptic encephalopathies (DEE). We report findings from a Phase 1 trial characterizing PRAX-562 safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) in healthy adults.
Method: PRAX-562-102 was a randomized, placebo-controlled trial in healthy adults (18-55 years). Part A evaluated 90mg PRAX-562 over 28 days (QD) vs. placebo. Part B evaluated oxcarbazepine (OXC) in combination with 120mg PRAX-562 (QD) over 28 days vs. OXC alone. PD effects were examined on quantitative (qEEG) and stimulated EEG (auditory steady state response, ASSR).
Results: 48 participants were enrolled (Part A, n=18 PRAX-562, n=12 placebo; Part B, n=14 0XC+PRAX-562, n=4 OXC+placebo). PRAX-562 concentrations exceeded the EC_{50} in the mouse maximal electroshock seizure model by 13-fold and were unaltered with OXC coadministration.
PRAX-562 was generally well tolerated in Part A. TEAEs were mostly mild or moderate (100% Part A; 96% Part B). Part B was stopped early after 5 participants receiving OXC+PRAX-562 developed TEAEs; one experienced 3 study drug-related SAEs leading to study drug discontinuation.
Exposure-dependent PD changes were observed on qEEG (all frequencies) and ASSR. Significant differences between placebo and PRAX-562 were observed in Part A on qEEG (Delta, P=0.0013; Theta, P<0.0001) and ASSR (phase-locking-factor, P=0.028; Evoked power, P=0.016), and in Part B participants receiving OXC+PRAX-562 vs. OXC alone on qEEG (Delta, P=0.012; Theta, P=0.018).
Conclusion: PRAX-562 was well tolerated in healthy adults at 90mg (Part A). Most AEs including SAEs in Part B were considered due to coadministration of projected supratherapeutic doses of PRAX-562 (120mg) with OXC. PK and tolerability findings are consistent with a wide therapeutic window for PRAX-562. PD findings indicate qEEG may be a sensitive translational biomarker of PRAX-562 sodium channel blockade.

Funding: Praxis Precision Medicines.

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Risk factor analysis for safe discontinuation of anti-seizure medication in children with epilepsy

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Purpose: This study aimed to identify reliable predictor for seizure recurrence after discontinuation of anti-seizure medication (ASM) in patients with pediatric onset epilepsy.
Method: This observational study was conducted at Asan Medical Center Children's Hospital in Korea using data which were retrieved from 594 patients with epilepsy followed up for more than 10 years in January 1997 to January 2010. The patients' medical records were retrospectively reviewed, and clinical outcomes were assessed based on the recurrence rate after discontinuation of anti-seizure medications.
Results: Total 150 patients has experienced one or more ASM discontinuation during 17.4 years of mean follow-up period. Among them, 104 patients had recurrence of seizure after discontinuation with 85.7%, 87.0%, and 48.5% of recurrence rate, respectively, in patient group with seizure-free period less than 2 years, 2 to 5 years, and 5 years of longer, before discontinuation. The structural etiology, developmental delay or intellectual disability, electroencephalography abnormalities at last follow-up, and shorter period of seizure freedom before discontinuation were significantly associated with seizure recurrence after discontinuation. In multivariable logistic analysis, the EEG abnormalities at last follow-up and seizure freedom period less than 5 years before discontinuation had statistically significant odds ratio of 3.10 (95% confidence interval, 1.32-7.20) and 7.13 (95% confidence interval, 3.08-16.5) for seizure recurrence.
Conclusion: Longer treatment period led to decrease in recurrence of seizure. Further study to weigh benefit and adverse events of anti-seizure medication is urgent.

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Feasibility, tolerability and efficacy of the ketogenic diet in children with drug-resistant epilepsy in South Vietnam

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Purpose: According to the World Health Organization, more than 50 million people have epilepsy. Among them, nearly 80% of epileptic patients live in developing countries and 75% of them do not have access to treatment. The ketogenic diet (KD) has been shown as an effective alternative for patients with drug-resistant epilepsy. Although it has been studied by few studies in Asia, no such studies have been conducted in Vietnam. The purpose of this study

was to verify the feasibility, tolerability, and efficacy of the KD in children with refractory epilepsies followed at a pediatric center in South Vietnam.
Method: Children with drug-resistant epilepsy followed at Children's Hospital No.2, Vietnam treated by KD were included in a prospective study from June 2019 to October 2021. Side effects, retention rate, number, and duration of seizures were recorded after 1, 3, 6, 9, and 12 months of KD. Patients were considered responders when a 50% seizure frequency was reached. Tolerance and acceptability of the KD were closely monitored.
Results: Forty-six children were included but KD was contraindicated for one patient with hyperlipidemia. Due to the COVID pandemic, we had to rely on internet exchanges to stay in touch with families. Meals had to be adapted to Vietnamese culinary habits. The retention rate decreased from 82.22% at 1 month to 40% at 12 months of follow-up. The incidence of side effects was 44.44% and occurred mainly during the first month. Fifteen patients out of 45 were considered responders after 12 months of treatment.
Conclusion: Our study was the first attempt to introduce KD in Vietnam. We demonstrated that this diet was feasible and well tolerated, despite its differences from Vietnamese culinary habits. The KD resulted in significant improvement in drug-resistant epilepsies and should be considered a alternative in a country where many patients lack access to recent treatments.

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NUS1 mutations caused Lennox-Gastaut syndrome related to unfolded protein reaction activation

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Purpose: *NUS1* encodes the Nogo-B receptor (NgBR), a highly expressed multifunctional protein in brain across the human lifespan. NgBR is critical for N-linked glycosylation, a regulator of unfolded protein reactions (UPR) pathway. So far, 38 mutations in *NUS1* have been reported in patients with neurodevelopmental disorder, such as loss-of-function mutations in developmental and epileptic encephalopathy and missense mutations in Parkinson`s disease. The relation between *NUS1* and Lennox-Gastaut syndrome and its pathogenic role should be investigated.
Method: We identified mutations of *NUS1* in a cohort of 165 Lennox-Gastaut syndrome (LGS) patients using trios-based whole exome sequencing, and evaluated the pathogenicity of the mutations with occurrence frequency, damaging predication, and computational modeling. Furthermore, we analyzed functional change of *NUS1* in cultured cells by overexpressing the mutant and knockdown of *NUS1*. Last, we constructed the *Nus1* knock-down and *Nus1* mutant knock-in *Drosophila* model to assess the relationship between the genotype and phenotype.

Results: We identified two *de novo* mutations of *NUS1* (c.792-2A>G and c.868C>T/p.R290C) in two unrelated LGS patients, showed a significantly high observed number of *de novo* mutations than expected in genome-wide ($P = 8.5 \times 10^{-7}$).The splice site mutation (c.792-2A>G) produced an inclusion of the DNA sequence of intron 4 between the exon 3 and 4, resulted in a premature termination codon gain.Knocking down of *NUS1* activated UPR pathway and resulted in apoptosis in 293T cells, and the wild-type but not the mutant (p.R290C) rescued the activation and apoptosis. Seizure rate and recovery time were significantly increased in *Nus1* knockdown and $Nus1^{R290C/+}$ flies with UPR activation. Electrophysiologic recordings showed that excitatory neurons in *Nus1*-deficient flies exhibited increased excitability.
Conclusion: These results demonstrated that mutants in *NUS1* caused LGS due to activating UPR pathway, which may be a common pathogenic role of NUS1 mutations implicated in epilepsy.

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Prevalence and clinical-EEG phenotypes of epilepsies in 70 patients with genetic syndromes

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Purpose: The aim of the present study was: -to recognize the epileptic and electroencephalographic (EEG) characteristics and neurological comorbidities of patients with defined genetic syndromes to identify any novel diagnostic markers useful to characterize specific conditions; -to evaluate relationships between epilepsy and neuropsychiatric phenotype.
Method: We included 70 paediatric and young adult patients (41 males, age range 1–24 years) with defined genetic syndromes with and without epilepsy; 32 patients had microdeletion or microduplication syndromes, 34 monogenic syndromes, 4 chromosomal disorders. For each patient we evaluated epileptic phenotype, EEG characteristics and comorbidities
Results: 82,9% of patients showed movement disorders, 44,3 % psychiatric disorders, 87,1% intellectual disability and among them 50,7% had severe intellectual disability. We noted the high prevalence of epilepsy in genetic syndromes (57.1%) and a significantly (p 0.001) higher frequency of epilepsy in subjects with monogenic alteration compared to other types. For 67.5% of patients, onset of epilepsy occurred within 3 years of age and more than one third (42,5%) had drug-resistant epilepsy.
42,6% of patients showed poor awake and sleep EEG organization and 85,3% of patients had interictal epileptiform abnormalities, more patients with epilepsy (100%) than patients without epilepsy (65,5%). We found a relationship close to significance (p 0.057) between frequency of interictal epileptic abnormalities and severity of intellectual disability. Non-epileptiform EEG abnormalities was observed in 52.9% of patients, specifically increased rhythmic alpha–beta activity in patients without epilepsy and slow focal activity in patients with epilep-

sy; this EEG-pattern had a significative relationship with epilepsy (p 0.001). Most patients with epilepsy showed a clinical picture consistent with Developmental Epileptic Encephalopathy.
Conclusion: Despite the variety of symptoms in the different genetic syndromes, we have observed some peculiar clinical and EEG findings shared by several genetic syndrome that can be useful in orienting diagnosis and management of care.

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A quinidine non responsive de novo KCNT1 mutation in a patient with epilepsy of infancy with migrating focal seizures

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Purpose: Our aim is to present the clinical course and outcome of a female patient suffering from epilepsy of infancy with migrating focal seizures (EIMFS) on the grounds of a de-novo heterozygous mutation in KCNT1 gene.
Method: This is a 5 year old female patient presenting with drug-resistant epilepsy, severe neurodevelopmental delay and autistic trait. Seizure onset occurred at the late neonatal period. EEG findings showed focal migrating epileptic activity and whole exome sequencing revealed a de novo mutation [c.800T>C(P.Met267Thr)] on KCNT1 gene. Multiple antiepileptic drugs (AEDs) were used, ACTH included. Oral quinidine was administered right after WES results at the age of 4 months with doses ranging from 6-80mg/kg/d. During her therapy our patient underwent frequent EKG and quinidine blood levels monitoring.
Results:
Our patient developed multi drug-resistant epilepsy with poor response to multiple AEDs. Quinidine was relatively well tolerated. Therapeutic levels (2-5μg/ml) were late achieved at doses 45mg/kg/d. The most significant adverse event was transient QTc prolongation at doses 45mg/kg/d. Furthermore, at dose of 80mg/kg/d she developed conduction abnormalities (LBBB) and cinchonism symptoms. Quinidine levels at that point were measured 6,7μg/ml. Since quinidine was failing to fully control her epileptic activity while causing adverse effects, therapy was gradually seized. Moreover, she developed persistent iatrogenic cortisol axis suppression due to ACTH treatment, still requiring hydrocortisol supplementation. Today, at the age of 5 years old and treated with valproate, lamotrigine and gabapentin our patient shows adequate seizure control but suffers from severe neurodevelopmental delay and autistic disorder.

Conclusion: Prompt seizure control in infants with KCNT1-related epileptic encephalopathy is necessary in order to achieve developmental progress. Response to quinidine, as targeted treatment of KCNT1-channelopathy presents heterogenity among patients. Larger cohort studies could lead to the development of a more specific KCNT1 channel-targeting inhibitor, providing better outcomes for patients with refractory epilepsy of this origin.

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Cognitive debrief of the clinical global impression of improvement for non-seizure symptoms measure in Dravet syndrome and Lennox–Gastaut syndrome: the caregiver's perspective

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Purpose: Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) are characterized by treatment-resistant seizures, developmental delay, and/or intellectual disability. Given that patients cannot selfreport, caregivers' feedback on the relevance and understandability of the Clinical Global Impression of Improvement for non-seizure Symptoms measure items, a clinician-reported outcome (ClinRO), is critical to ensure the measure is fitfor-purpose and that caregivers can assist with completion. We report the results of interview debriefs with caregivers of patients with DS or LGS about the ClinRO measure, which assesses within-patient change for communication, alertness, and disruptive behavior.
Method: Caregivers were recruited through advocacy organizations (January to March 2022). After screening, caregivers completed a concept elicitation and cognitive debriefing interview. A qualitative analysis plan was developed for interview analysis.
Results: Twenty-one caregivers debriefed the measure (caregivers: 100% female; mean age, 41 years); all were parents of patients (patients: DS, n=10; LGS, n=11; 61.9% male; mean age, 10.1 years [DS, 7.3 years; LGS, 12.7 years]). Caregivers described their child's status easily using the baseline item descriptions and used the response scale to describe levels of change. All caregivers understood the communication item (n=21), and most found it relevant (n=20). All understood and found the alertness item relevant. All understood the disruptive behavior item (n=20), and most found it relevant (n=19) (one caregiver was not debriefed). Most caregivers ranked each item as ≥7 on an importance scale of 0–10 and reported that minimal improvement in each item would be meaningful for their child.
Conclusion: Caregivers' feedback indicated that the measure items represented highly relevant non-seizure outcomes and were easy to understand and use; minimal improvement in each item would represent meaningful outcomes in these core areas. Further analysis is planned following completion of ongoing phase 3 studies.

Study funded by Takeda Pharmaceutical Company Limited.

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Factors affecting the outcome of the first EEG in children with suspected epilepsy: a retrospective age-related comparison between awake and sleep recordings

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Purpose: A first unprovoked EEG has a low sensitivity to diagnose childhood epilepsy. This can increase by repeated investigations with provocations or sleep recordings. To explore the EEG diagnostic yield in children of different ages we analyzed demographic and clinical factors that affected decision of EEG method, and factors associated to the occurrence of epileptiform activity in primary EEG recordings.
Method: We retrospectively analyzed demographic and clinical data from 1097 EEGs performed as a first recording in children with suspected epilepsy. Children were divided in ages 0-5, 6-11 and 12-17 years. EEGs were classified by method: wake recordings with or without provocations, and sleep recordings, sleep induced by deprivation or melatonin premedication. Multiple (multinomial and logistic) regression was used to explore factors associated to EEG method and epileptiform activity.
Results: EEG with provocations or after sleep deprivation was more likely in older children. In children with underlying neurological disease or intellectual disability, resting EEG without provocations was more likely. In EEGs performed within 72 hours post-seizure, resting recordings were significantly more common. In suspected absence epilepsy, EEG with provocations was significantly more likely than in other epilepsies. Epileptiform activity was positively associated with age, sleep, neurological disease, and intellectual disability. In melatonin-induced sleep EEGs epileptiform activity was significantly more common compared to other types of sleep EEG. That probability increased in children with neurological diseases or intellectual disability and decreased in neurobehavioral disorders.
Conclusion: Clinical symptoms, seizure semiology and comorbidity affect the choice of EEG method. Sleep EEG is advantageous as the first registration in children: they fall asleep easily and the occurrence of epileptiform discharges increases. Children with neurological diseases or intellectual disability can benefit from doing sleep EEG as wake EEG can be challenging. Melatonin EEG is recommended due to higher sensitivity for epileptiform discharges compared with other types of sleep EEG.

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Development of the Dravet disease scale with associated neuropsychiatric disorder (D-DAND) interview

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Purpose: Dravet Syndrome(DS) is a developmental and epileptic encephalopathy(DEE) characterized by the seizures' onset before 15 months old with the appearance of global neurodevelopmental disorder encompassing intellectual, psychiatric disability. These main comorbidities make the administration of standardized evaluations difficult and no suitable tests are available to evaluate properly the patients with DS' development. We developed an ecological, holistic, multiaxial tool D-DAND with an outlook of a lifespan assessment based on caregivers' interview and aiming to detect changes in patients with DS considering seizures and comorbidities.
Method: This study is the joint work of two family associations of DS and two expert centers in rare/complex epilepsies. The team includes four child-neurologists, one child-psychiatrist, and three neuropsychologists. We drew on the known comorbidities to elaborate the D-DAND score. The interview is organized in 9 neuropsychiatric domains and 1 medical domain(clinical/electrophysiological data). For the tool's validation, 6 standardized tests were administered concomitantly. A follow-up session is planned to assess the reliability of D-DAND interview. The inclusion criterion was the DS diagnosis with SCN1A mutation with a minimal age of 3.
Results: We included 69 patients from January 2021 to January 2023. The average age of the cohort is 12.8 years (y)(median:12.5 y; min-max:[3-34]. The DAND interview lasts 35 minutes(min) on average(median:30 min; min-max:[15-60]). Seventy-three percent of interviews occurred in one session whereas the others in 2. They were conducted with a neuropsychologist at the hospital(68%), videoconferencing(26%), or both(6%). They were administered to mothers(79%), fathers(6%), or both(13%). All interviews were fully answered as well as the concomitant tests.
Conclusion: We developed D-DAND interview for comprehensive neuropsychiatric assessment for DS patients adapted to their cognitive and behavioral profile. The protocol has been already conducted on a substantial number of patients. Future steps will aim to explore its reliability to detect individuals' changes and expand it to other infancy onset DEEs.

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EEG graph theory biomarkers for epilepsy diagnosis in children with SeLECTS

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Purpose: Electroencephalography (EEG) can be considered the gold standard diagnostic technique for self-limited epilepsy with centrotemporal spikes (SeLECTS). Recent studies built functional brain networks from EEG recordings to understand patterns of connectivity between brain areas of interest.
In this study, we applied graph theory metrics to functional brain networks of children with SeLECTS, and unmatched first-degree family members. The overall goal was to identify a possible heritable quantitative biomarker for this syndrome and to lateralize the seizure onset.
Method: A 20-second artefact-free segment was extracted from EEG recording (19 channels) collected from SeLECTS (N=16; mean age: 9.5 years; male: 11) and unmatched first-degree family members (N=16; mean age: 10.3; male: 9). Six children had focal seizures that originated from the right hemisphere (mean age: 7; male: 4), whilst six children had focal seizures that originated from the left hemisphere (mean age: 8; male: 4). For each participant an individual brain network was created in the low-alpha frequency band (6-9 Hz) using phase locking value. The median of four graph theory metrics (mean strength, variance of strength, average betweenness centrality, average eigenvector centrality) was compared between children with SeLECTS and their first-degree relatives using the non-parametric Wilcoxon rank sum test.
Results: The variance of strength was statistically significantly higher in SeLECTS compared to first-degree relatives (p-value = 0.03). In addition, there was a trend in the variance of strength of the left versus the right hemisphere. Comparisons between the two groups when considering the mean strength, average eigenvector centrality, and betweenness centrality were not significant (p-value > 0.05).
Conclusion: The preliminary findings of this study show that brain network metrics computed from EEG recordings have the potential to aid in the diagnosis of SeLECTS. Further studies in this direction could offer an additional quantitative tool for the diagnosis of SeLECTS.

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Focal seizures as a confusing onset of recurrent MOGAD (myelin oligodendrocyte glycoprotein antibody disease)

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Purpose: MOGAD is a demyelinating syndrome with the presence of antibodies against myelin oligodendrocyte glycoprotein, is, next to multiple sclerosis and the neuromyelitis optica spectrum, one of the manifestations of the demyelinating process, more common in the pediatric population. MOGAD can take a variety of clinical forms: acute disseminated encephalomyelitis (ADEM), retrobulbar optic neuritis, often binocular (ON), transverse myelitis (TM), or NMOSD-like course (neuromyelitis optica spectrum disorders), less often encephalopathy. The course may be monophasic (40-50%) or polyphasic (50-60%), especially in the case of persistently positive anti-MOG antibodies. Very rarely, the first manifestation of the disease,

preceding the typical symptoms of MOGAD by 8 to 48 months is focal seizures with secondary generalization, without typical demyelinating changes on MRI of the head . The paper presents a case of a 17-year-old patient whose first symptoms of MOGAD were focal epileptic seizures in the form of turning the head to the right with the elevation of the left upper limb and salivation. Seizures occurred after surgical excision of a tumor of the right adrenal gland (ganglioneuroblastoma) and then, despite a normal MRI of the head and the exclusion of onconeural antibodies in the serum and in the cerebrospinal fluid, a paraneoplastic syndrome was suspected. After treatment with i.v. steroids, immunoglobulins, after 8 plasmapheresis procedures and initiation of antiepileptic treatment, the seizures subsided and there were no other neurological manifestations for 9 months. Only subsequent relapses of the disease with typical radiological and clinical picture (ADEM, MDEM, binocular ON) allowed for proper diagnosis and then treatment of the patient both during relapses and by initiating supportive treatment.

Method: *
Results: *
Conclusion: The patient's case allows us to analyze the multi-phase, clinically diverse course of MOGAD, and above all, indicates the need to expand the diagnosis of epilepsy towards demyelinating diseases: determination of anti-MOG and anti-AQP4 antibodies.

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Risk factors for epilepsy in children in communities with high prevalence in Cameroon

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Purpose: In Cameroon, most cases of epilepsy begin in childhood. Currently, there's little or no data on the risk factors of epilepsy in children in Cameroon. Our study aimed to generate baseline data on risk factors for epilepsy in children so as to informed interventions to reduce the prevalence and burden of childhood epilepsy.
Method: We conducted a cross sectional and descriptive study in 3 communities with high epilepsy prevalence. Using a 5-item questionnaire that has been validated for the screening of epilepsy by Diagana et al., we screened for children with epilepsy. The parents and/or caregiver of each child was subsequently interrogated about the child's exposure to different risk factors of epilepsy prior to the onset of epilepsy. The children were physically assessed thoroughly and their medical records examined.
Results: One hundred and sixty two(162) children met the criteria for epilepsy and were included in the study. Most participants were female (52%) as against 48% for males. The age range of the participants varied between 3months-17 years. Most of the participants (46.4%) had epilepsy from unknown etiology. A positive family history was the main risk factor in 26.4% of cases. We also identified a significant number(28) of cases of epilepsy which were due to preventable risk factors with complications from meningitis (11 cases), cerebral malar-

ia (9 cases) and neonatal asphyxia (5 cases) being the main preventable risk factors. Six children met the clinical criteria for onchocerciasis-associated epilepsy.
Conclusion: Most cases of childhood epilepsy in our study had no identifiable cause. A significant number of childhood epilepsy cases can be prevented hence more awareness and education on preventable risk factors for epilepsy should be done. Further studies involving genetic tests and brain imaging should be conducted to provide more data on the risk factors of epilepsy in children in Cameroon.

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Focal cortical seizures and extrapyramidal tongue and jaw tremor in a four-month-old boy following acute infarction of the left frontoparietal cerebral cortex

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Purpose: We aim to provide insight into combined epileptic and extrapyramidal movements following acute infarct.
Method: Case is reported through history, exam, and diagnostics, including video images, magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), and video electroencephalogram (EEG) data. An extensive review of the literature was conducted.
Results: Here we report for the first time a case of acute-onset tongue and jaw tremor without EEG correlation and focal seizures with right head and eye version and EEG correlation in a four-month-old boy following acute infarction of the left frontoparietal cerebral cortex. This case follows prior reports of a 42 and an 82-year-old man with a similar movement disorder following infarction of the left frontal cerebral cortex and is in contrast with the well-established localization of palatal, tongue, jaw or lip tremor, or myoclonus to brainstem injury.
Conclusion: Seizures were most likely related to stroke in the setting of infant neurophysiology; seizures are common presentations of stroke in the neonatal and infant population. Extrapyramidal movements, however, are rare after cortical injury in any age group. Typically, these tremors are associated with lesions involving the basal ganglia, brainstem, and/or cerebellum involving the Guillain-Mollaret triangle (red, inferior olivary, dentate nuclei, and the fiber pathways that link these structures to each other). There are two case reports of tongue tremors in acute cortical infarcts in 42- and 82-year-old men. Both cases were associated with left frontal infarcts involving the pre-central gyrus without imaging abnormalities of the basal ganglia, cerebellum, or brainstem. These cases emphasize the importance of circuitry beyond structural localization when evaluating a patient with an uncommon neurological presentation. Future research may concentrate on the neurophysiology of cortical connections, which could illuminate the mechanism of extrapyramidal movements seen after cortical lesions.

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Radiomics analysis in pediatric patients with MRI-negative temporal lobe epilepsy

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Purpose: To investigate whether radiomics features differ between patients with epilepsy and healthy controls, and whether there are differences that can identify pediatric patients with magnetic resonance imaging (MRI)-negative temporal lobe epilepsy.
Method: Data from 40 patients with hippocampal sclerosis (HS) and 50 healthy controls were used to construct a radiomics model. A total of 1618 radiomics features from the affected hippocampal and extrahippocampal regions were compared with features from healthy controls and the unaffected side of patients. Using a stepwise selection method with a univariate *t*-test and elastic net penalization, significant predictors for identifying TLE were separately selected for the hippocampus (H+) and extrahippocampal region (H−). Each model was independently validated with an internal set of MRI-negative adult TLE patients (n = 22) and pediatric validation cohort with MRI-negative TLE (n = 20) from another tertiary center; diagnostic performance was calculated using area under the curve (AUC) of the receiver-operating-characteristics curve analysis.
Results: Forty-eight significant H+ radiomics features and 99 significant H− radiomics features were selected from the affected side of patients and used to create a hippocampus model and an extrahippocampal model, respectively. Texture features were the most frequently selected feature. Training set showed slightly higher accuracy between hippocampal (AUC = 0.99) and extrahippocampal model (AUC = 0.97). In the internal validation and external validation sets, the extrahippocampal model (AUC= 0.80 and 0.92, respectively) showed higher diagnostic performance for identifying the affected side of patients than the hippocampus model (AUC=0.67 and 0.69).
Conclusion: Radiomics revealed extrahippocampal abnormality in the affected side of patients with TLE and could potentially help to identify MRI-negative TLE.

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Genomic analysis in Chilean pediatric patients with drug-resistant epilepsy

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Purpose: The genetic diagnosis of pediatric patients with drug-resistant epilepsy (DRE) constitutes an important challenge. By implementing exome sequencing coupled with bioinformatic

analysis in Chilean DRE patients with unresolved etiology, we aimed to increase our diagnostic capacity, identify novel monogenic causes, , and expand our clinical knowledge of pediatric DRE

Method: We recruited 20 Chilean pediatric DRE patients between 0-18 years old. All participants had a prior genetic epilepsy panel, performed in a clinical laboratory, with negative results or variants of unknown significance. Exome sequencing, quality control procedures and variant calling was performed with the Agilent SureSelect V6 library following the GATK2 protocols. Bioinformatic annotation was carried out with ANNOVAR software. The interpretation of variants was performed following the American College of Medical Genetics (ACMG) criteria. Clinical data were aggregated into a REDCap registry for further analysis. The study has the consent and approval of the institutional ethics committee and all parents gave written informed consent

Results: The diagnosis of epilepsy occurred prior to 24 months of age in 50% of cases. and the average time with seizures was 7 years (1-18). After exome sequencing, from an average of 140,000 initial variants detected, we selected 4-12 candidate variants per individual for variant interpretation using a set of filtering criteria that included: variants in candidate epilepsy genes, high bioinformatic scores and absence in general population databases. We identified three novel pathogenic variants (CSNK2B, SCN1A, ALDH7A1) and nine likely pathogenic variants that await do novo confirmation. The remaining three cases carried only variants of uncertain significance.

Conclusion: Our approach detected pathogenic and likely pathogenic variants in 80% of cases and generated a rich phenotypical database of pediatric DRE. This is the first study in Chile, focused on pediatric patients with DRE and shows the increased diagnostic yield of WES over epilepsy panels

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Smaller ipsilesional thalamus in children after perinatal arterial ischemic stroke can predict epilepsy but not its severity

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Purpose: Epilepsy is one of the most frequent consequences after perinatal stroke. It develops in 6 – 71 % of patients with perinatal stroke depending on vascular subtype and length of follow-up. It is still unclear in which children with perinatal stroke the likelihood of epilepsy is greater.

The aim of our study was to evaluate the size of the thalamus in children with perinatal arterial ischemic stroke (AIS) in relation to poststroke epilepsy.

Method: Methods and study group. The study group consisted of patients identified from the Estonian Pediatric Stroke Database and fulfilled the inclusion criteria: 1) neuroradiologically confirmed diagnosis of neonatal or presumed perinatal AIS; 2) birth at ≥36 weeks of gestational age; 3) follow-up study with 3T MRI scan with 3D T1 investigation; 4) clinical fol-

low-up of at least 4 years. The size of the thalamus was evaluated using volumetric analysis by segmentation. Severe epilepsy was defined as one of following: monthly or higher seizure frequency, presence of status epilepticus or electrical status epilepticus in sleep, need for polytherapy.
Results: Results. The study included 29 patients (15 children with neonatal AIS and 14 with presumed perinatal AIS); 10 of them developed epilepsy at a mean age of last follow up of 13.2 years, while 6 of them had severe epilepsy. Mean time of follow-up MRI was 10.6 years. Volumetric analysis by segmentation revealed smaller (p= 0.0004) ipsilesional thalamic volume in the group of children who developed epilepsy compared to those who did not develop epilepsy. There were no differences (p= 0.4587) regarding thalamic size between the patients with a severe course of epilepsy and the rest of the patients who developed epilepsy.
Conclusion: Conclusion. Evaluation of the size of the ipsilesional thalamus in children with perinatal stroke can predict the development of epilepsy after AIS.
The work was supported by PRG1912.

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Healthcare resource utilisation in Lennox-Gastaut Syndrome: interim results from a European real-world point-in-time study

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Purpose: Lennox-Gastaut syndrome (LGS) is a rare, severe childhood-onset developmental and epileptic encephalopathy.
Current published data quantifying healthcare resource utilisation (HCRU) in LGS are country specific. We aimed to describe HCRU by the LGS population in Europe.
Method: Data were drawn from the Adelphi LGS Disease Specific Programme, a real-world, point-in-time survey conducted in France, Germany, Italy, Spain, and the UK commencing July 2022. Neurologists (child and adult) completed record forms for consecutively consulting patients with LGS, providing data on demographics and LGS-related seizure and non-seizure HCRU (including consultations, assessments, hospitalizations) in the 12 months prior. Data was delineated into age groups: <6, 6-18 and >18 years. Outcomes presented are based on an interim cutoff date of 24/11/22.
Results: Overall, 40 neurologists completed records for 139 patients with a physician confirmed LGS diagnosis (<6y: n=18; 6-18y: n=63; >18y: n=58). The mean [SD] age was 19.1y [11.8], 55% were male and mean [SD] age at first seizure was 4.2y [4.1].

In the previous 12 months, mean [SD] total number of consultations regardless of speciality was 9.3 [14.9] (<6y: 16.3 [22.5], 6-18y: 8.8 [9.1]; >18: 6.7 [14.7]). In this time-period, mean [SD] number of assessments conducted was 6.0 [5.2] (<6y: 10.8 [8.1], 6-18y: 5.7 [4.0]; >18: 4.3 [3.0]); Non-surgery hospitalization (≥ 1) reported for 17% of patients (<6y: 44%; 6-18y: 17%; >18y: 7%); and 39% reported ≥ 1 emergency room visit (<6y: 67%; 6-18y: 38%; >18y: 31%).
Conclusion: A higher number of healthcare resources were accessed by the youngest cohort, coinciding with mean age at diagnosis. Altogether, a LGS diagnosis was associated with a high burden of care which negatively impacts healthcare costs. These data suggest an unmet need for therapies that effectively target a holistic approach, to alleviate the LGS burden of illness and positively impact HCRU. Funded by UCB Pharma.

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Ketogenic diet in nonketotic hyperglycinemia in a Colombian hospital: outcomes of 10 years retrospective review

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Purpose: Nonketotic hyperglycinemia (NKH) is the inborn error of glycine metabolism which results in accumulation of large quantities of glycine in body tissues including the brain.
At the west of Antioquia, we have a cluster of patients whit NKH, all whit onset in the neonatal period manifest as progressive lethargy evolving into profound coma and marked hypotonia, seizures, with or without burst suppression pattern on EEG. The majority have the mutation c.2714T>G;(C2714T>G)*pVal905Gly in GLDC gen.
No treatment is effective in changing the natural history of developmental delays, spasticity, and intractable epilepsy. Few reports have indicated that the Ketogenic Diet (KD) in association with standard therapy can lead to important reductions in seizure activity in patients with neonatal NKH.
The aim of this study is describing the response to KD treatment in 24 patients whit NKH.
Method: Descriptive study that included 24 of the 43 patients with NKH diagnosed between 2012 and 2022 that were in KD treatment.
Qualitative variables included were described as frequencies, quantitative variables those with a normal distribution were described as means.
Results: Onset of symptoms was first 7 days of life in 75%, and 41% at the first day of life.
83% have tractopaty in brain resonance, and 20.8% have thin corpus callosum70.8% had glycine peak in spectroscopy.
First electroencephalogram(EEG) had multifiocal epileptiform activity in 37.5% and burst suppression pattern in 29.1%. Two patients had inicial EEG normal.
Age at the start of KD was 29.1% at first month and 50% in first 6 months.
Three patients are seizure free, 83.3% had improvement in seizure control, and 41% improves attentiveness. Two patients didn't have response to KD.

Conclusion: KD it's an good option to treat patient whit severe forms of NKH.
It's important to establishing protocols for diagnosis, multidisciplinary treatment, looking for expanding the knowledge of this disease.

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Design of a double-blind, randomized, cross-over, placebo-controlled phase 2 trial of basimglurant as adjunctive therapy in patients with seizures associated with tuberous sclerosis complex (GALENE)

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Purpose: Emerging evidence indicates that the overactivation of metabotropic glutamate receptor type 5 (mGluR5) is involved in a number of central nervous diseases, in particular tuberous sclerosis complex (TSC). Here we describe the design of an ongoing phase 2 trial assessing basimglurant, a selective negative allosteric modulator (NAM) of mGluR5, in patients with TSC.
Method: Basimglurant is a potent mGluR5 NAM with selectivity > 1000-fold compared to other mGluR NAMs. An optimized modified-release oral formulation demonstrates robust brain occupancy, good bioavailability and half-life, and allows once-daily dosing. In previous clinical trials, basimglurant has been well tolerated in children and adolescents.
GALENE is a Phase 2B, multicenter, 30-week, prospective, cross-over, double-blind, randomised placebo-controlled trial (NCT05059327) to evaluate the efficacy and safety of basimglurant. Children, adolescents, and young adults with a documented history of TSC with seizures currently taking at least 1 antiseizure medication (ASM) are being enrolled. After a 4-week stabilization (Period 1), participants are randomized to basimglurant or placebo for 12 weeks (Period 2). After a 2-week wash-out (Period 3), they are randomized to the other treatment arm for another 12 weeks (Period 4). Eligible participants are offered access to a one-year open-label extension period.
Results: Enrolment is ongoing aiming to enrol 54 participants. The primary endpoint is monthly seizure counts during the 12-week maintenance dosing in Period 2 and Period 4. Secondary efficacy endpoints include the impact on functioning, number of treatment responders, and longest seizure-free interval. In addition to safety and tolerability assessments, the impact on seizure type is assessed.
Conclusion: The GALENE trial will characterise the efficacy and safety profile of the novel mGluR5 NAM basimglurant in patients with uncontrolled seizures associated with TSC.
This trial is funded by Noema AG.

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Serum interleukin-1β and tumor necrosis factor - α levels in children with febrile seizures

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Purpose: To identify the correlation between serum interleukin-1beta , tumor necrosis factor-alpha and febrile seizures in children.
Method: Fifty children between the age of 4 months and 5 years with simple or complex febrile seizures (FS) and 39 controls were included in this case-control study from 2021 to 2022. Concentrations of serum IL-1β and TNF-α were measured using enzyme-linked immunosorbent assay (ELISA).
Results: The median serum TNF-α level in the FS group was significantly higher than that in the control group (19.54 ng/ml vs 8.86 ng/ml, $p < 0.05$). Higher median serum IL-1 β levels were detected in the FS group comparing with controls (13.38 pg/ml vs 3,0 pg/ml, $p < 0.001$). Also we have found the correlation between IL 1 β an recurrence of seyzures (r_{xy} +0,70), but no correlation with TNF.
Conclusion: Our study supports the hypothesis that cytokines have played a role in the pathogenesis of febrile seizures and the number of seizures correlates with level of IL-1 β.

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Outcomes in clinical trials for West syndrome

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Purpose: The aim of this study is to determine the selection of outcomes in clinical trials evaluating treatment interventions for patients with West Syndrome.
Method: A search was performed on the ClinicalTrials.gov database on December 28, 2022, using the keywords: “West Syndrome,” “Infantile Spasm,” and “Hypsarrhythmia.” The search looked for interventional studies in Phase 2 or 3, in pediatric patients with West Syndrome.
Results: The initial search identified 30 trials. Four were excluded due to the wrong condition. One study was a phase 1 trial, two were phase 4 trials, and three did not evaluate treatment interventions for West Syndrome. One study was excluded due to a lack of information regarding outcome measures. The final analysis included 19 phase 2 or phase 3 trials in different stages of completion.
For the primary outcomes, 47.4% (9/19) of the studies assessed only clinical response, 26.3% (5/19) measured electroclinical response, and 10.5% (2/19) considered clinical and electrical response as separate outcomes. There were also differences within clinical, electrical, and electroclinical response definitions. Additionally, 21.1% (419) of the studies also had primary outcomes related to adverse events.

Conclusion: In conclusion, this study found a heterogeneity of outcome measures used in trials evaluating treatment interventions for West Syndrome. This highlights the need for consensus on the best outcome measures to assess treatment response in this condition.

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Generalized tonic and tonic-clonic seizures in the first year of life: are they truly generalized and correlated with the epileptic syndrome?

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Purpose: Truly generalized tonic (GTS) or tonic-clonic (GTCS) seizures in the first year of life are rare and not always traceable to a specific epileptic syndrome. We evaluated possible correlations between ictal EEG patterns and outcome severity.
Method: We selected patients from one day to 12 months of age with GTS or GTCS who underwent video-EEG between 2011 and 2021. We divided the sample into two groups, Self-Limited Neonatal/Infantile Epilepsy (SeLNIE) and Developmental and Epileptic Encephalopathy (DEE), matching neurological evolution, genetic results, and neuroimaging features. Age at seizure onset, age at EEG recording, and EEG features of the first GTCS and GTS recorded were assessed.
Results: Forty-one patients with a mean age at seizure onset and a mean age at EEG recording of 4.48 ±3.76 and 6.02 ±3.35 months, respectively, were included. Thirteen patients (32%) presented with SeLNIE, 28 (68%) with DEE. GTCS were present in 13/13 of SeLNIE (100%) e in 11/28 of DEE (39%). GTS were only found in 17/28 (61%) of DEE. Focal onset was seen in 24 patients, all with GTCS. Of these, 13/13 (100%) had SeLNIE and 11/28 (39%) had DEE. Postictal generalized electroencephalographic suppression (PGES) was observed in 18 patients, 9/13 (69%) with SeLNIE and 9/28 (32%) with DEE. The logistic regression statistical analysis showed a positive correlation between PGES and GTCS (OR=7.778, p=0.007). T-test analysis revealed a statistical difference between the mean duration of GTCS and GTS and between the mean duration of both seizure types in the two groups (p-value <0.05). The mean seizure duration was higher in GTCS than in GTS and the mean duration of GTCS was longer in SeLNIE than in DEE.
Conclusion: GTS were only found in DEE. Most GTCS in the first year of life had a focal onset, despite a generalized clinical semiology. Longer GTCS were the domain of SeLNIE.

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Retrospective analysis of resective epilepsy surgery for pediatric patients with non-neoplastic lesions: A series of 32 patients

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Purpose: Resective epilepsy surgery is an effective treatment modality for patients with intractable epilepsy. Its benefits are proven in adults and promising results are also achieved in children.
Method: We evaluated clinical and radiological features and postoperative results of 32 patients, that underwent resective epilepsy surgery with a mean follow up period of 30 months. Patients with neoplastic lesions are excluded from the study.
Results: Among 32 patients, 10 were female and 22 were male. Mean age was 8 (1-17). Majority of the lesions were in the temporal lobe (50%) followed by frontal (41%), parietal (6%) and occipital (3%) lobes. Ten patients were found to have mesial temporal sclerosis. 18 patients were diagnosed with cortical dysplasia, further classified with Blumcke Classification. There were four type IA, one IC, two IIA, three IIB, three IIIC and one IIID. Four patients couldn't be attributed to any type due to lack of specimen. Remaining patients were diagnosed with Landau Kleffner syndrome, Rasmussen encephalitis, electrical status epilepticus during slow sleep (ESES) and gliozis. There were no major complications except transient worsening of existing motor deficits in four patients, which resolved shortly. Seizure outcome wad determined in seven patients (22%) Engel I and in nine patients (28%) Engel II. Three patient died due to other comorbidities.
Conclusion: Resective surgery is an efficacious option for selected patients suffering from intractable epilepsy. With benefits of invasive monitoring, cortical mapping and neuronavigation technologies, it is a safe and effective treatment modality.

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Detection of tonic seizures using a multimodal wearable device with behind-the-ear EEG

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Purpose: Promising results in the development of wearable seizure technology are reported for absence seizures and generalized tonic-clonic seizures. However other seizure types are important in childhood drug-resistant epilepsy. Lennox-Gastaut syndrome for example, presents with tonic and atonic seizures, but also myoclonic seizures and atypical absences. For these patients a more complex detection system is necessary. In this patient group there is a

need for seizure detection wearables for multiple reasons: seizure counts in drug trials, clinical decision making and SUDEP prevention.
Method: We tested a multimodal seizure detection wearable (Sensor Dot, Byteflies), combining EEG, ECG, EMG and accelerometer signals, for the detection of tonic seizures. The device was used in parallel with 24 hour video EEG (gold standard). The current study is an extension of previous projects (SeizeIT1, SeizeIT2) for clinical validation of the wearable (Plug 'n Patch project, clinicaltrials.gov, NCT04584385). Children between 4 and 18 years old were included.
Results: Nine children, including 6 Lennox-Gastaut patients, had tonic seizures during measurement. 66 tonic seizures were detected over 192 hours and 14 minutes of recording. Seizure duration ranged between 2 seconds and 2 minutes and 29 seconds. Eighty-five seizures (88%) were visually recognizable on the wearable data, when combining EEG, EMG and accelerometer. Blind annotations of the wearable data by a neurologist did not give satisfying results (F1 score < 0.5), mostly due to high false alarm rates caused by artefacts. Sensitivity reached 35%, rising to 50% for seizures lasting at least 10 seconds.
Conclusion: We investigated the detection of tonic seizures in children with severe epilepsy syndromes including Lennox-Gastaut using a multimodal wearable device. A personalized approach looking at EEG, EMG and accelerometer signals will be needed to identify the stereotypic sequence of electrographic and movement features of tonic seizures. A machine learning approach combining modalities could help discriminating seizures from artefacts.

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Pharmacokinetics of co-administered ganaxolone and cannabidiol in healthy adults

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Purpose: Ganaxolone, a neuroactive steroid and positive allosteric modulator that targets both synaptic and extrasynaptic $GABA_A$ receptors, is FDA-approved for the treatment of seizures associated with CDKL5 Deficiency Disorder (CDD) in patients 2 years of age and older. Given ganaxolone and cannabidiol may be co-administered in the treatment of CDD-associated seizures, a pharmacokinetic (PK) study evaluating the potential for drug-drug interactions was conducted.
Method: In this single center, open-label, fixed-sequence, 2 treatment study, healthy adult subjects received 600 mg oral ganaxolone (50 mg/mL) on Day 1, 12.5 mg/kg oral cannabidiol BID (25 mg/kg/day, Epidiolex®) on Days 4-15, and a single oral dose of 600 mg ganaxolone co-administered with the morning dose of 12.5 mg/kg cannabidiol on Day 13. Ganaxolone and cannabidiol plasma concentrations were determined using validated bioanalytical methods. Routine safety monitoring was conducted throughout.
Results: Of the 21 healthy adults who were enrolled, 20 completed the PK component of the trial. Preliminary analysis of the PK endpoints indicated that ganaxolone C_{max} and AUC_{0-t} were approximately 10% and 20% lower, respectively, when co-administered with cannabidiol. No unexpected safety findings were reported.
Conclusion: Ganaxolone PK parameters C_{max} and AUC_{0-t} were slightly reduced when co-admin-

istered with cannabidiol. These changes are not expected to be clinically significant. No new safety findings were identified. These data suggest that clinically significant pharmacokinetic interactions with coadministration of ganaxolone and cannabidiol are unlikely.

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A unique association between GAMT deficiency and PTEN mutation

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Purpose: Guanidinoacetate methyltransferase (GAMT) deficiency is a rare inherited creatine deficiency syndrome characterized by global developmental delay, intellectual disability, and epilepsy. Phosphatase and tensin homolog (PTEN) gene is a tumor-suppressor gene located on chromosome 10. Mutation in the PTEN gene can cause Cowden syndrome, an autosomal dominant disorder characterized by development of multiple hamartomas, macrocephaly, brain overgrowth and an increased risk of developing cancer. This paper aims to describe the association between GAMT deficiency epileptic spasms and macrocephaly.
Method: We present the case of a 5 year old boy with a history of epilepsy and macrocephaly for which we provide the findings from the neurological exam, electroencephalographic monitoring, brain MR spectroscopy, whole exome sequencing, and metabolic screening.
Results: His personal history revealed macrocephaly and megalencephaly since birth, neurodevelopmental delay, autism spectrum disorder, and epilepsy. Epileptic spasms appeared at 4 months old with a good response to Nitrazepam and Topiramate, the patient being seizure-free since 6 months old. The EEG showed a hypsarrhythmic pattern. The metabolic screening revealed GAMT deficiency. The patient underwent a brain MR spectroscopy that revealed a reduced creatine signal and supplementation with creatine and ornithine was initiated. Favorable neurodevelopmental evolution was achieved. Whole exome sequencing showed a variant of uncertain significance (VUS) in the PTEN gene, position c.29.G>T, p.(Ser-10Ile), which could be associated with Cowden syndrome type I.
Conclusion: This case shows a rare association between a metabolic disorder and a VUS mutation involving the mTOR inhibitory pathway, with overlapping features. We emphasize the importance of genetic and metabolic testing in pediatric epilepsy patients, especially in the presence of a heterogenous electro-clinical picture. Moreover, VUS mutations should not be overlooked especially in the presence of prominent clinical features.

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Oxidative stress, metalloproteinase and inflammatory cytokines in children after seizures

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Purpose: Oxidative stress, inflammatory cytokines and metalloproteinase (MMPs) play a pivotal role in the pathogenesis of epilepsy. This study examined the underlying mechanism of epilepsy in children, especially with respect to the roles of MMP's, interleukin-1β (IL-1β), IL-6, neuron-specific enolase (NSE), erythropoietin (EPO), C-reactive protein (CRP) and free radicals.
Method: Ninety-four children from 9 months to 12 years of age with epilepsy participated in this study. We analyzed saliva parameters for MMPs and free radicals. The concentrations of CSF NSE, 1L-1β, IL-6, EPO and CRP were measured by specific ELISA methods.
Results: Mean salivary LDH concentration in controls was 252.6 ±12.0 IU/L, dropping by 58% (p = 0.005) in epileptic group. Mean salivary values of peroxidase activity and SOD activity level were 445 ± 11 mU/mL, 1.66 ± 0.13 U/mL respectively, in controls, increasing by 9% (p = 0.05) and by 40% (p = 0.04) in epileptic group. Mean salivary MMP 9 concentration was 0.043 ± 0.011 in controls, increased by 28% (p = 0.058) in epileptic group. The mean concentrations of NSE, IL-1β, EPO and CRP in the epileptic group showed a significant increase ($P < 0.01$) as compared with the control group. The mutual correlations of NSE, 1L-1β, IL-6 and CRP were also analyzed. Results showed that there were positive correlations between the markers and seizure severity and frequency.
Conclusion: Our results enhance the understanding of underlying mechanism of epilepsy as reflected by the results with high rate of oxidative metabolism, coupled with increased inflammatory cytokines and CRP levels in epileptic group. The changed activity of metallo-proteinase, NSE, 1L-1β, IL-6 and EPO level, may be beneficial for the pathophysiology study of epileptic seizures. The results will also help in the identification of clinically useful, reliable biomarkers and diagnosis of pediatric epilepsy.

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A rare case of houge type, X- linked CNKSR2 deletion resulting in developmental disorder and epilepsy

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Purpose: We present this case in order to enable a better understanding and improve ability to ordinate adequate treatment in individuals with CNKSR2-related neurodevelopmental disorders and epilepsy. This report aims to help clinicians in diagnosis of this rare microdeletion and further genetic counseling.
Method: Blood samples were collected for array comparative genomic hybridization (aCGH) analyses from both the parents and the child. Neurological examination, cranial magnetic resonance imaging (MRi) and electroencephalography (EEG) were also performed.
Results: The 4 years old female patient was slow in achieving milestones and presented early-onset seizures. Her psychomotor development evidently delayed withing the first year of

life and further. Neurological examination showed axial hypotonia and underdeveloped expressive speech. Cranial magnetic resonance imaging revealed mild periventricular leukomalacia (PVL) and the EEG recordings showed rare isolated epileptiform discharges. Genetic analyses revealed maternally inherited 688-kb deletion of chromosome Xp22.12, including CNKSR2 gene, by array comparative genomic hybridization (aCGH).
Conclusion: In this case report, we identified a microdeletion in the CNKSR2 gene with previously described phenotype, rarely mentioned in literature. Deletions in connector enhancer of kinase suppressor of Ras-2 (CNKSR2) located on the X chromosome (Xp22.12) result in epilepsy phenotype and developmental delay with variable intellectual impairment (Mei D et al. BMC Medical Genetics 2020; 21:69). CNKSR2 gene is highly expressed only in the brain resulting in phenotypic effects restricted to the brain. The child gave favorable therapeutic response to Valproic acid and attends speech and occupational therapy in order to achieve the best possible outcome.

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PCDH19 syndrome: case report of a novel mutation in a girl with epilepsy

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Purpose: PCDH19 gene encodes an adhesion molecule that induces type A GABA receptors, crucial for neuronal differentiation, migration and maturation, and responsible for Epilepsy and Mental Retardation Limited to Females (EFMR), a syndrome with onset during early childhood that resembles Dravet Syndrome. Inherited in an X-linked fashion, mainly affects females, who present clusters of febrile and afebrile focal onset seizures before 3 years of age that decrease over time and cognitive impairment. In most cases, seizures are refractory and require polytherapy. We present a patient with a variant not previously described aiming to improve the evidence for future genotype/phenotype analyses.
Method: Describe a case of EFMR, it´s clinical characteristics and an overview of therapeutic management.
Results: A 20-month-old female patient, the third child of healthy non-consanguineous parents debuted with complex febrile seizure and unprovoked seizures. Levetiracetam produced behavioral side effects, valproate showed low response. Mild speech delay was identified but improved rapidly with therapy. Serum amino acids, urine organic acids, ammonia, arterial blood gasses, lactate, videoEEG and brain MRI were normal. Seizure clusters persisted but now she could tell before motor symptoms arose, suggesting focal onset and prompting a switch to oxcarbazepine and clobazam with improvement in seizure control. NGS revealed a likely pathogenic missense variant (PCDH19:p.L150P), confirming the diagnosis.
Conclusion: The clinical picture of EFMR is heterogeneous; childhood-onset epilepsy, cluster seizures, fever sensitivity, and intellectual disability or behavioral disturbances are key, all of which were observed in our patient. In our experience, dual therapy with carbamazepine and clonazepam has allowed good seizure control, which may be novel because sodium channel

blockers can worsen symptoms in up to 20% of patients. This variant of PCDH19 highlights that its genetic approach should be considered in girls with infantile-onset seizures and developmental delay, with manifestations resembling Dravet syndrome, but the SCN1A gene test was negative.

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Predicting upcoming interictal epileptiform discharges with deep learning

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Purpose: Interictal epileptiform discharges (IED's) are a transient abnormal feature of hyper-excitable cortex often seen in the epileptic brain. In patients with focal epilepsies, the area of cortex that generates IED's – the *irritative zone* – typically includes, but is not limited to, the seizure generating *epileptogenic zone*. IED frequency is cyclical, and this variability may be due to local or global changes in brain function; for instance, there is evidence of increased IED occurrence during sleep, suggesting a link between sleep states and IED's. Furthermore, within the irritative zone, IED's have been shown to be preceded by an increase in low-frequency oscillations (1-8Hz) (*Westin et al., 2020*), which are sensitive markers of sleep stage changes.
Method: Stimulation is currently used diagnostically to identify patterns of cortical connectivity as well as areas with abnormal hyperexcitability. We hypothesise that delayed responses to single-pulse electrical stimulation (SPES), which occur preferentially in epileptogenic tissue, have a temporal correlation with IEDs arising from a dynamic epileptic network. With this in mind, we present the use of deep learning to predict IEDs 200-400ms prior to their occurrence. Recordings from twelve children who underwent intracranial stereoEEG (SEEG) for seizure localisation were analysed. Inputs to the networks were one second of SEEG from up to 200 channels.
Results: AUROC scores of up to 0.85 were achieved, and the location of pre-IED changes had an overlap with the irritative zone. Whilst the final networks were patient-specific, the network structure allowed for pre-training across patients, reducing the amount of required training data.
Conclusion: Model performance was competitive with an existing machine learning classifier (AUROC: 0.76). Crucially, we predict that applying SPES when the brain is in a pro-IED state will increase the likelihood of a delayed response, implying that temporally targeting SPES

based on brain state may increase their diagnostic yield.

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Use of complementary and alternative medicine in the management of pediatric epilepsy at Geneva University Hospitals

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Purpose: Little is known on the use of non-pharmacological treatments in the management of pediatric disorders in Western countries. Our aim was to study the current situation in Geneva regarding the use of complementary and alternative medicine (CAMs) in the management of epilepsy and to determine whether certain practices stand out more than others in order to study them more specifically.
Method: This cross-sectional study used a structured questionnaire distributed to parents of patients with epilepsy attending our pediatric neurology consultation in Geneva University Hospitals. Data collection took place during consultations between November 2020 and December 2021. Questions addressed the use of CAMs, including a section examining the intention with which parents privileged these approaches and whether beneficial or side effects were reported.
Results: We obtained 100 responses, but not all items on the questionnaires were completed. A majority of the questionnaires were completed by women (n=64, 66%) and by parents whose culture is predominantly Swiss (n=58, 59.8%). CAMs were frequently used: 69.1% had already benefited from alternative medicine. For example, homeopathy was used by 39 (40%) of the respondents and osteopathy by 29 (30%). Phytotherapy (n=23, 24%), kinesiology (n=19, 20%) and aromatherapy (n=18, 19%) were also commonly used. When parents use CAMs for themselves, they often tend to use them for their children (n=48 children, 89%). 2 (3%) of respondents reported adverse events in relation to CAMs use, such as increased seizures with essential oils or vomiting after osteopathic manipulations.
Conclusion: An important part of the population of children with epilepsy followed at a highly specialized pediatric tertiary care center in Geneva, Switzerland, uses CAMs in the management of the disease. It seems important to take this into account in the practice of pediatric neurology and above all to specifically study the mode of action, the efficacy, and the safety of these approaches.

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Investigation of some biomarkers in paediatric patients with seizures and underlying neurodegenerative, metabolic diseases and structural epilepsy

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Purpose: To study the blood level of some biomarkers in paediatric patients with different type of epilepsy in different neurological diseases to better understanding of neuronal mechanisms underlying the neurological diseases and seizures in children and biomarkers of this process.
Method: In 44 children (12 months-17 years) we measured the level of autoantibodies to glutamate receptors NR2A(NR2AaAB), GluR1(GluR1aAB), S100 protein, neuron specific enolasa (NSE) and 3-nitrothyrosine(3-NT) in blood serum and plasma of 16 patients with neurodegenerative/neurometabolic diseases(ND) (Organic/Amino Acid Disorders, Krabbe Disease, mucopolysaccharidosis II , neuronal ceroid lipofuscinosis etc), in 5 with mitochondrial disorders(MD), in 10 with epilepsy after the ischemic stroke(ISE), in 8 with cerebral palsy and epilepsy(CPE) and in 5 with multiple sclerosis(MS).
Results: The results obtained by us are as follows: the high level in NR2AaAB was found in all groups, especially in patients with ND 3,89±0,74ng/ml and MS3,32±0,5(N<2.0ng/ml), less elevation was in children with structural epilepsy CPE/ISE. The significant elevation in GluR1aAB was in children with MD 3,57±0,2 (N<2,0ng/ml).The S100protein highest level was revealed in patients with structural epilepsy in CP(153,13±41) and MD (149,8±32 ng/l), less elevated in ISE(N<90 ng/l). NSE high level was in MD(34,71±8µg/l)(N<10). 3-NT level was high in all groups, especially in structural epilepsy in CP/IS. The elevated level of NR2AaAB in MS patients need further investigation.
Conclusion: Children with MD and structural epilepsy(CPE/ISE) shows more numbers of elevated blood biomarkers than patients from anothe studied groups, it may reflect the neuronal destructive processes and possible neuroinflamation in these patients in higher grade comparing with other groups. Biomarker research faced several challenges, however the blood-based biomarkers research in neurological disorders need further evaluation in clinical trials to impact on diagnosis and treatment of patients.

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Brain connectivity in a large cohort of paediatric patients with or without epileptic spasms within the first year of life

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Purpose: There are currently no recognized early biomarkers of seizure outcome for patients with epilepsy onset in the first year of life, especially for epileptic patients with or without

spasms. In this study we analyze the possible role of quantitative EEG analysis in predicting seizure outcome.
Method: Scalp video-EEG recordings were collected retrospectively between 2008 and 2020 in Bambino Gesù Children Hospital. 3606 children performed a video-EEG within the first year, regardless of the cause. We divided the sample based on neurological examination and epilepsy diagnosis.
A subsequent quantitative analysis on the first EEG will be performed. We will extract two EEG features (power spectrum and Entropy) from three different EEG subgroups: patients with epilepsy starting in the first year of life without spasms, patients with spasms starting in the first year of life and patient without epilepsy with normal neurological examination. A statistical regression analysis will be computed to study the correlation between the electro-encephalographic features of each EEG group and seizure outcome at last follow-up.
Results: 928/3606 (26%) patients (541 M and 387 F) were diagnosed with epilepsy in the first year of life. 221/928 presented with epileptic spasms and 707/928 had epilepsy without spasms. 506/3606 (14%) had normal EEG, normal neurological examination, and no epilepsy diagnosis at last follow-up. 2172 (60%) had epilepsy onset beyond the first year of life or an abnormal neurological examination, without epilepsy. The average age at first EEG was 5.89±0.90 months
Conclusion: We will perform the quantitative EEG analysis in the three groups in order to early differentiate different epileptic subtypes and delineate a possible EEG biomarker for future research.

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How the description of myoclonic epilepsy with ragged-red fibers (MERRF) has been changed through the last decades?

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Purpose: MERRF syndrome is a rare syndromic mitochondrial disorder (MID) with a broad phenotypic but narrow genotypic heterogeneity. However through the last decades the some clinical findings has changed the initial clinical chart described. The objective is to present all the clinical features described until nowadays, being more opened when the suspicious about MERRF is the mind of the clinician, in order to avoid the mitochondrion- toxic agents, including mitochondrion-toxic ASMs.
Method: For a long time the four canonical features myoclonus, generalized epilepsy, ataxia, were the most relevant clinical findings and the confirmation is done by a ragged-red fiber myopathy. The most frequent seizure type in MERRF is generalised myoclonic seizure but also focal myoclonic, focal atonic, focal clonic, generalised tonic-clonic, generalised atonic, generalised myoclonic-atonic, typical absences, or tonic-clonic seizures.By searching the literature, data for this review were identified.
Results: It can involve any of the following:
*Brain: Myocloni, Epilepsy, Migraine, migraine-like, Cognitive impairment, dementia, Optic

atrophy, Tremor, Cerebellar ataxia, Depression, Dementia, Parkinson syndrome, Dystonia, Dyskinesia, Bulbar involvement, Stroke-like episodes, Leucencephalopathy, Bilateral thalamic lesions, Psychiatric disorder, Leigh syndrome, Elevated CSF protein. Skeletal muscle: Myopathy, Respiratory involvement, Exercise intolerance, Elevated creatine-kinase, Myalgia, Ptosis, Ophthalmoplegia. *Eyes: Visual impairment, Pigmentary retinopathy, Cataract. *Ears: Hypoacusis.
*Endocrine organs: Diabetes, Short stature, Hypothyroidism. *Heart: Arrhythmias, Cardiomyopathy.
*Gastrointestinal: Chronic pancreatitis, Paralytic ileus, Diarrhea, Vomiting, Dysphagia. *Peripheral nerves: Polyneuropathy.
*Bone marrow: Anemia. *Skin: Multiple lipomatosis, Psoriasis. *Other Lactic acidosis, Arterial hypertension, Fibrous bone dysplasia, Hyperlipidemia, Clubfeet.
MERRF plus includes 4 four canonical features and abnormalities of the CNS, peripheral nerves, eyes, ears, endocrine organs, heart, gastrointestinal tract or skin.
Conclusion: Since the phenotypic manifestations of the m.8344A > G and the m.8363G > A variants may be mild or subclinical. Detection of the multisystem nature of the syndrome is crucial as particularly seizures and cardiomyopathy may strongly determine the outcome.

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EEG education in child neurology and neurodevelopmental disabilities residencies: a survey of U.S. and Canadian program directors

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Purpose: To characterize the current EEG education practices in child neurology (CN) and neurodevelopmental disabilities (NDD) residency programs in the U.S. and Canada.
Method: A 30-question e-survey focused on characteristics of residency programs and their EEG teaching practices was sent to all 88 CN and NDD residency program directors listed in the Accreditation Council for Graduate Medical Education (ACGME) and Canadian Residency Matching Service websites.
Results: We received responses from twenty-nine (n= 29/88; 33%) residency programs, most located in the U.S. (83%). All 29 programs were hosted in a total of 26 institutions, all of which had a CN program, and three of which also had an NDD program. Most programs were university hospital-based (90%). EEG rotations involved the clinic/outpatient setting (83%), epilepsy monitoring unit (EMU) (76%), and inpatient setting (excluding EMU) (72%). During a typical 1-month EEG rotation, residents typically read 16-30 (31%), 31-45 (31%), 46-60 (14%),

or >60 (24%) EEGs. Types of EEGs read included routine (100%), prolonged routine (72%), continuous (66%), EMU (55%), and ambulatory (38%). The mean number of EEG weeks required to graduate was 7.3. Most programs (93%) did not have a minimum number of EEGs residents are required to read and generate a preliminary report to fulfill EEG rotation requirements. Almost two-thirds of programs (62%) reported not using objective measures to assess EEG competency.
Conclusion: Our survey results detail characteristics of resident EEG education among CN and NDD residency programs in the U.S. and Canada. We suggest systematic implementation of objective measures to teach EEG to residents and evaluate trainee EEG competency.

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Epilepsy is a prominent symptom in Rett syndrome

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Purpose: Rett syndrome (RTT) is a severe neurogenetic-developmental disorder. Manifestations include regression of motor and language skills, loss of purposeful hand function, onset of hand stereotypes and epilepsy.
We studied a cohort of 14 children with Rett syndrome, looking at epilepsy and its management.
Method: The study was conducted at the KK Women's & Children's Hospital Singapore. Approval was obtained from the Institute's Research Board.
Results: There were 14 children with RTT whose age ranged from 3 years to 25 years. Twelve of the 14 children were typical RTT. MECP2 mutations were detected in 10 children, 4 missense mutation and 6 nonsense mutation. One typical RTT had mutations in both the MECP2 and FOXG1 genes. Both cases of atypical RTT tested negative for MECP2mutations; one had mutations in the CDKL5 gene. Twelve children had epilepsy, with onset of epilepsy between 3 and 5 years. (stage II and III) All seizure types were seen, the commonest being generalized tonic clonic, tonic and myoclonic. Seizures were largely refractory requiring polytherapy. Additionally, many children had non-epileptiform events. A variety of antiepileptic drugs (AEDs) was used, including Sodium valproate, Clobazam and Levetiracetam. EEG abnormalities included slowing of background and multifocal epileptiform discharges.
Conclusion: Epilepsy is a prominent symptom in RTT. No specific AED is proven effective. Majority of the patients require polytherapy. EEGS, particularly video-eegs, are important diagnostic tools in RTT because they allow for the distinction between true seizures and non-epileptic events.

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Sport in the Hospital to promote physical and psychological wellbeing in children with epilepsy

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Purpose: People with epilepsy have been historically excluded from sports and exercise, usually due to fear and ignorance about the benefits and risks associated with such activities. Available evidence suggests that active engagement in sports may improve quality of life and cardiovascular health, and decrease interictal epileptiform discharges after exercise. On the strength of this evidence, the purpose of our study was to describe a sports enhancement program carried out in CWEs in a pediatric hospital.
Method: We recruited 17 children (M:6, F:11; MAge: 13.5 yrs) in charge at the Neurology Unit that participated in sports activities in small groups once a week, for 6 weeks in total. A certified personal trainer with a physiotherapist and a clinical psychologist led the intervention. Each encounter ran for 1,5 hour, spread over 50 minutes of physical activity and the remaining socialization time. We assess motor coordination, balance and muscle strength, mood and quality of life both before (T0) and after (T1) the program.
Results: We found an overall improvement trend in all the physical domains: visual manual coordination +29.04%, muscle strength +12.21% and balance +7.4'. Psychological wellbeing shows a quite positive trend on anxiety reduction (GAD-7 T0: M 4.55 vs T1: M 3.57, M -0.98), depression reduction (PHQ-9 T0: M 4.00 vs T1: 3.29, M -0.71), and health related quality of life improvement in children (PedsQL Self report T0: M 87.07 vs T1: 87.56, M +0.49; EQ-5D-5L Self report T0: M 86.15 vs T1 90.56, M +4.41).
Conclusion: This preliminary data shows a beneficial effect on physical and psychological wellbeing in CWE's after a 6 encounters program of sportive activities in Hospital. Physical exercise programs should be promoted by clinicians in CWE's as per recent evidences and international guidelines as a path to extensively improve the quality of life and care of those children.

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National care pathway for pediatric epilepsy patients in Croatia and Slovenia

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Purpose: The national care pathway for pediatric patients with epilepsy in Croatia and Slovenia does not exist. Early and appropriate diagnosis with the most precise therapeutical approach saves time and money and most importantly improves disease outcomes and quality

of life for patients and their families. The aim of this report is to assess current care pathways in pediatric patients with epilepsy.
Method: Two ERN EpiCARE centers and tertiary care hospitals in Croatia and Slovenia formulated current care pathways and proposed optimal changes to improve the clinical pathway for epilepsy in pediatric patients.
Results: There is wide variation in access to specialized care across Croatia and Slovenia due to national health organizations as well as geographical causes. After a first suspected seizure, a patient is referred to an emergency service at a primary level where they are seen by a general practitioner. Most patients are then referred to secondary or immediately to tertiary level care where they are seen by a specialist in child neurology. Most pharmacoresistant epilepsy patients are referred to the National referral center or EpiCARE center for further evaluation and possible referral to epilepsy surgery, which is not available in the two designated countries.
Conclusion: With current models of care, there is a lack of a clear national pathway, and it is important to address barriers in patient flow through the clinical pathway. While most epilepsy care can be provided at primary and secondary levels, there are some services that must be provided in a specialized center, especially for patients with a learning disability, rare and complex epilepsies, and pharmacoresistant epilepsies. Improving methods of information sharing could facilitate early diagnosis and specialist networking. Additionally, a national epilepsy registry would greatly facilitate communication between clinicians and improve patient care. Step down from tertiary centres should be offered in all uncomplicated cases.

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EPISTOP clinical trial data set re-use with statistical methodologies tailored for clinical trials in rare diseases (EPISTOP IDEAL)

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Purpose: Epilepsy is the most common neurological feature of Tuberous sclerosis complex and is highly refractory. TSC is also associated with neuropsychiatric disorders. EPISTOP clinical trial aimed to validate the effect of preventive versus late conservative standard therapy. This preventive therapy resulted in a better outcome in seizures and co-morbidities. This trial included a randomized and an observational nonrandomized preventive and standard groups that were pooled. EPISTOP-IDEAL aims to consolidate the primary endpoint results using bias assessment and external data and to strengthen the results of some secondary endpoints.

Method: **Development regarding level of evidence linked to randomization procedures:** We use the allocation bias model to study the impact on time to event data and to quantify the impact of bias on the study results and derive an estimate of the bias effect for future study design.
Methods for extrapolation: A parametric bootstrap test has been developed to test the similarity of hazard and survival curves between two independent groups of patients. The tests will be applied to validate the pooling of the preventive and conventional treatment groups.
Methods to assess and overcome uncertainty in estimates: We will formulate the adapted version of the Fill-it-up approach to pool EPISTOP observational and randomized trial data.
Results: We expect that by re-using EPISTOP data to evaluate the uncertainty of the results in order to derive the biased corrected test result. We expect to improve the statistical evidence particularly for secondary endpoints and to validate the pooling of both data, and to identify the most sensitive response variable. We will develop statistical models to overcome the uncertainty caused by bias in measurements enabling us to optimize future clinical trial planning.
Conclusion: The results will underlie the importance of accelerating the collaboration between clinicians and methodologists to promote the use of tailored methodologies for rare diseases clinical trials.

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Survey of Italian rehabilitation plan in patients with Dravet Syndrome: what we have and what we need

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Purpose: To describe the rehabilitation approach used in Italian Dravet syndrome patients.
Method: An anonymous cross-sectional retrospective online survey was performed between August and October 2019, addressed to families of patients with DS. The survey was carried with the support of "Gruppo Famiglie Dravet Associazione ONLUS", that distributed the survey-monkey link to all the 174 contacts of families of the network and spread the Survey through association Facebook page.
Questions on demographic data, clinical features (epilepsy features, neurological disorders and comorbidities), and treatment (antiseizure medicaments and rehabilitation approach) were included.
Individual anonymized data were exported as "Excel" worksheet and descriptive statistical measures were computed.
Results: The survey received 88 responses. 52 complete responses were collected and divided according to age: 14 between 2-10 yrs; 16 between 11-14 yrs; 12 between 16-19 yrs and 10 over 20 yrs.

All patients presented seizures with different frequency, 80% were treated with multiple ASM and 20% with monotherapy.
Cognitive deficits were reported in all subjects, behavioural problems in 94.2% of patients, language deficits in 88.4% and motor disorders in 82.6%.
At the survey time all children younger than 10 years had rehabilitation; the percentage decreases to 70% among adolescents, and to 40% in adults. Rehabilitation approach consisted of psychomotor therapy and speech therapy during childhood; during adolescence, cognitive behavior therapy, associated to speech- or physio-therapy was performed in 32%,occupational therapy in 25%.
Adults performed only physio therapy.
Conclusion: The rehabilitation plan is fully performed during childhood compared to adolescence and adulthood. However, the course of DS, characterized by the childhood onset of cognitive/behavioural and motor
disorders, suggests the need for an integration of the rehabilitation plan with targeted and personalized approach, starting from childhood and continuing across lifespan. This could improve the outcome and quality of life of patients and their families.

1285

Overlapping features in epilepsy of infancy with migrating focal seizures (EIMFS)

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Purpose: To describe the electroclinical features, aetiologies and outcomes of infants with EIMFS, highlighting overlapping features with other developmental and epileptic encephalopathies
Method: Retrospective review of clinical notes and video EEG recordings of five consecutive infants (four girls) diagnosed with EIMFS between January 2020 until December 2021
Results: Four infants had neonatal-onset seizures (at median 6.5 days), consisting of focal tonic, clonic or autonomic seizures, associated with a burst-suppression EEG pattern soon after onset in three and a focal EEG pattern that changed to burst-suppression within a month in one infant. One infant presented at 5 months with epileptic spasms associated with hypsarrhythmia on EEG. Seizures evolved to include alternating focal motor seizures in all and epileptic spasms in one infant. Ictal recordings demonstrating independent right and left hemisphere seizure onsets and migrating patterns were recorded in all, at 1-7 (median 3.5) months of age; additionally, concurrent interictal EEG showed burst-suppression pattern in two infants. Aetiologies include a novel *KCNQ2* mutation, an *SCN2a* mutation, an *AMT* mutation (associated with high serum glycine, in keeping with non-ketotic hyperglycinemia) and a *9q33.3q34.11* deletion that involved *STXBP1* gene. WES for the girl with infant-onset seizures was negative. Seizures were never controlled in the infant with *SCN2a* who succumbed at 3 months. Following trials of multiple anti-seizure medications (ASMs),including ketogenic diet in four infants, two infants eventually became seizure free (*KCNQ2* on carbamazepine; WES

negative on topiramate & clobazam), one had significant seizure reduction (*STXBP1* on valproate & vigabatrin) and the infant with non-ketotic hyperglycinemia continued to have daily seizures (despite ASMs, dextromethorphan & sodium benzoate). All had global developmental delay.
Conclusion: In our experience, EIMFS seemed to evolve from or appeared concurrent with electroclinical features of early infantile developmental & epileptic encephalopathy or infantile epileptic spasms syndrome. Outcome may ultimately be determined by the underlying aetiology.

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Point-of-care EEG for seizure detection: comparison of electrode positions in two channel EEG

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Purpose: The use of few electrodes EEG for seizure detection in pediatric emergency departments is developing rapidly and is emerging to an important point-of-care bedside test. The aim of this study was to investigate if frontotemporal electrode positions (F7-T5 and F8-T6) are superior to usual centroparietal electrode positions (C3-P3 and C4-P4) in seizure detection in point-of-care two channel EEG.
Method: We reviewed a convenient sample of previously recorded long-term EEG (International gold standard 10-20 EEG system) with prior detected electrographic seizures in children (38 participants, median age 8.71). The EEG parameters were converted into two, two channel EEG (F7-T5 and F8-T6 versus C3-P3 and C4-P4) and were analyzed blinded to the long-term EEG findings.
Results: Our main results showed that there was no difference in seizure detection in frontotemporal electrode positions compared to centroparietal electrode positions (Sensitivity for both 64%). Furthermore, we found no significant correlation of age, seizure duration, bilaterality, rhythmic activity, wakefulness or seizure localization with false positive or false negative rates in both frontotemporal and centroparietal electrode positions. Only spike frequency showed significant correlation with false positive rates (p-value 0.036) and false negative rates (p-value 0.008) in frontotemporal electrode positions.
Conclusion: Frontotemporal and centroparietal electrode positions do not differ in detection rate of epileptic seizures and both positions may be used for point-of-care EEG bedside testing in pediatric emergency settings.

1342

Functional evaluation of gain-of-function mutations of endo- /lysosomal CLC transporters involved in human neurological diseases

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Purpose: Genetic mutations in the genes encoding neuronally expressed chloride / protein antiporters of the CLC family cause a multitude of neurodevelopmental and neurodegenerative diseases, in many cases associated with epilepsy. CLCN6 encodes ClC-6 that is predominantly expressed in neurons, where it is localized to late endosomes (Jentsch and Pusch, 2018). Mutations in CLCN6 are associated with neurodegenerative and lysosomal storage disorders. A *de novo* missense variant in CLCN6 might be associated with early infantile epileptic encephalopathy (Peng *et al.*, 2018). More recently, the *de novo* variant ClC-6^{Y553C} has been described in 3 patients, one of which had epileptic episodes at 4 years of age (Polovitskaya *et al.*, 2020). Heterologous expression of ClC-6^{Y553C} elicited a strong gain-of-function (GOF) phenotype compared with ClC-6 WT (Polovitskaya *et al.*, 2020; Zifarelli *et al.*,2022). A similar electrophysiological behavior is seen for the ClC-7^{Y715C} variant, associated with organomegaly and delayed development (Nicoli *et al.*, 2019). ClC-6 and ClC-7 share 45% of homology identity, and both tyrosines are conserved among them.
Method: In order to test if the GOF of the two mutations could be seen in the corresponding CLC, we characterized the ClC-7^{Y577C} and ClC-6^{Y781C} mutants, using whole cell patch clamp of transfected HEK cells.
Results: Interestingly, while ClC-7^{Y577C} recapitulated the GOF seen in the corresponding ClC-6^{Y553C}, activity of ClC-6^{Y781C} was actually reduced compared to WT ClC-6.
Conclusion: These results contribute to a better understanding in the molecular mechanism of these two highly related chloride transporters and their involvement in human diseases.

1345

Does the use of more restrictive diagnostic criteria in Lennox-Gastaut Syndrome improve the identification of the etiology?

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Purpose: Lennox-Gastaut Syndrome (LGS) is a developmental epileptic encephalopathy with defined electro-clinical features, although there are few series analysing its etiology in recent years after the improvement of genetic and neuroimaging techniques. The purpose is to determine the frequency, etiology and characteristics of a series of children with LGS
Method: Retrospective analysis of children with LGS at a pediatric epilepsy hospital. Only those who met strict diagnostic criteria were included: multiple types of drug resistant seizures (tonic nocturnal seizures); cognitive impairments; diffuse slow spike and wave and generalized paroxysmal fast sleep activity on EEG
Results:

38 patients out of a database of 1600 children with epilepsy met SLG criteria (2.2%).
The etiology was structural in 13 (33.3%), 3 with known genetic cause (TSC2 and DEPDC5 gene alterations), of which, 90% were preceded by Infantile Epileptic Spasms Syndrome (IESS). 14 patients (35.9%) had a genetic etiology (MECP2 duplication, Down syndrome and point mutations in DDX3X, TCF4, CDKL5, CHD2, MECP2, KCNB1, SMC1A, NARS1). Of these, 35.7% had a history of IESS.
Only in 11 patients (30.8%) no known cause was found after an etiological study (exome, brain MRI and metabolic study). Of these patients, 54.5% had previous normal psychomotor development and a later onset of epilepsy
Conclusion: It is more common to find etiology in children with LGS with current diagnostic techniques (69.2%) than classically described in the literature, with genetic causes accounting for 43.5%, probably related to the application of more restrictive diagnostic criteria.

1359

Cognitive and behavioural prognostic factors in children with epileptic encephalopathy with continuous spikes and waves during sleep (CSWS)

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Purpose: Epileptic encephalopathy with continuous spikes and waves during sleep (CSWS) is characterized by decline of intellectual functioning and neurobehavioral disorders due to strong activation of epileptiform activity in the electroencephalogram (EEG) during sleep. The aim of this study is to deepen the description of the cognitive-behavioral profile of children with CSWS and their long-term prognosis and to identify potential risk factors for greater severity.
Method: Retrospective study of children diagnosed with CSWS between 2009 and 2023 followed using a standardized protocol including serial clinical, neuropsychological and EEG evaluations.
Results: We included 63 individuals with a median age at CSWS onset of 5,5 years and a follow up period ranging from 8 months to 14 years. The median Intellectual Quotient (IQ) at the moment of last neuropsychological assessment was 78, range 40 to 124. A lower IQ was observed among children with structural etiology, whereas we were unable to demonstrate a correlation between IQ and the duration of the CSWS pattern in the EEG in our cohort. Six individuals fulfilled criteria for Landau Kleffner syndrome, 2 for visual agnosia and the rest had a more generalized decline in cognitive skills. We found an improvement in cognitive and behavioural functioning after controlling CSWS, with significant residual sequelae. 15 of 63 individuals (24%) were given methylphenidate, with a general positive response and no remarkable adverse effects. Besides a distinctive cognitive and behavioural profile, we have

also detected peculiarities in social aspects that emerge and evolve during the course of the disease.
Conclusion: CSWS is an epilepsy with devastating cognitive, behavioural and social sequelae. With the aim of reducing the neuropsychological impact, early detection is crucial and treatment should be considered an emergency. Children with CSWS should be referred from the moment of diagnosis to highly specialized epilepsy units able to provide experienced neuropsychological monitoring and support.

1386

Brivaracetam, an effective treatment for refractory typical absences

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Purpose: Absences associated with 2,5-4 Hz generalized spike-wave can be present in different epileptic syndromes. Rarely these absences are refractory to valproic acid, lamotrigine or etosuximide but in these cases there are no recommended treatment. Brivaracetam is a third-generation antiepileptic drug that is effective for convulsive tonic-clonic and myoclonic seizures in idiopathic generalized epilepsies, but there is no data about its efficacy in typical refractory absence seizures.
Method: Retrospective study about efficacy of brivaracetam in children with refractory typical absence seizures (associated with 2,5-4Hz ictal pattern) in paediatric hospital in Spain with follow-up of at least 12 months.
Results: 208 patients out of a database of 1600 children with epilepsy were treated with brivaracetam (13%) and only was administered in 11 children with refractory typical absences (0,6%). The mean age of theses patients was 11,6 years. The mean anti-seizure medication proven before brivaracetam was 5 (range: 2-11). Mean dose of brivacetam was 200 mg/day (range: 150-300) for >50 kg children or 3,8 mg/kg/day (range:2,5-5,5 mg/kg/day) for <50 kg children. The epileptic syndrome was unspecified idiopathic generalized epilepsy in 8, generalized developmental and epileptic encephalopathy in 2 and Jeavons syndrome in 1. Brivaracetam was effective in 45% (5/11): 1 patient with complete resolution of absence seizures, 3 with >90% reduction of seizures frequency and 1 with >50% reduction of seizures frequency. 2 brivaracetam responder patients had taken levetiracetam before and it was not effective. We did not identify any characteristica associated to a better response to brivaracetam. No secondary effects were reported
Conclusion: Brivaracetam can be an effective treatment for children with refractory typical absences

1404

Epileptic encephalopathy of genetic etiology associated with Kabuki syndrome type 2: case report

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Purpose: Case report of patient with Epileptic Encephalopathy associated with Kabuki Syndrome type 2, with worse evolution compared to reported cases.
Method: Observational, prospective, descriptive study of a patient with Lennox Gastaut Syndrome and Kabuki Syndrome type 2
Results: 12-year-old female, who started seizures symptoms at 6 years with electroencephalogram(EEG) with focal interictal epileptiform activity and poor development of sleep graphoelements.
Started antiepileptic treatment at 9, presenting focal seizures and episodes of Status Epilepticus with Lennox Gastaut Syndrome(LGS)EEG pattern. Brain MRI shows bilateral hippocampal volume decrease and mild ventriculomegaly.
Genetic study was positive with pathogenic variant of KDM6A gene or Kabuki Syndrome(KS) type 2.
After 2 years, she begins weekly atonic and daily generalized seizures, treated with clobazam,phenobarbital and topiramate. History of adverse drugs reactions.
24 hours Monitoring EEG shows LGS pattern and 60 seizures(10 electroclinical/50 electrical) with generalized,atonic and motor.
Diagnoses after pre-surgical study are Refractory Epilepsy, Non-lesional, Combined Epilepsy, genetic etiology with KS type 2, LGS and severe intellectual disability. Therefore, Palliative Epilepsy Surgery with Callosotomy is considered.
Favorable post-surgery evolution, seizures decrease(frequency/duration),according to Engel IB classification and cognitive and EEG improvement.
Conclusion: Epilepsy describe in Kabuki Syndrome is focal, with good response to antiepileptic drugs and in the most of the cases it is associated with type 1(pathogenic variant of KMT2D gene)
Our case presented worse evolution of epilepsy in relation to literature, refractory, LGS, adverse drug reactions and alterations in brain MRI, that could correspond to changes associated with seizures.
Epilepsy Surgery is considered part of the treatment in Epilepsy. It can reduce negative effects of seizures and antiepileptic drugs, improves cognition, reduces mobility and mortality and presents better outcome earlier, which in our case obtained good results in seizure control, cognitive improvement and quality of life.
An early pre-surgical assessment would be advisable in these cases and the etiology of the epilepsy being decisive.

1405

Late diagnosis of pyridoxine dependent epilepsy, review and 2 case report

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Purpose: Characterize presentation of piridoxine-dependent epilepsy of late diagnosis.
Method: Observational, prospective, descriptive study of two patients with piridoxine-dependent epilepsy with late diagnosis.
Results: Our sample consists of 2 patients, 6 years old, sisters, with refractory epilepsy, combined epilepsy, high-dose levetiracetam-lamotrigine treatment. Normal Brain MRI.
They have daily seizures, mainly generalized and Status Epilepticus episodes(benzodiazepine SOS 1-2 times/month).
Started Clobazam and Modified Atkins Ketogenic Diet, previously used, reducing frequency and duration of seizures.
Genetic study shows a variant of uncertain significance, c.458T>C (p.Ile153Thr), was identified in ALDH7A1, gene associated with autosomal recessive pyridoxine-dependent epilepsy.
Pyridoxine test results positive with decreased interictal-ictal epileptiform activity and subsequent normalization.
They start piridoxine(100 mg every 8 hours), suspend ketogenic diet, decreasing seizures and normalizing electroencephalogram. They discontinue lamotrigine.
The first patient presented status associated with febrile respiratory symptoms, requiring a high dose of pyridoxine(500 mg/day for 3 days).
They maintain pyridoxine,clobazam and levetiracetam, presenting focal seizures, without status.
The first case adds carbamazepine and the second lacosamide, achieving freedom seizures.
Conclusion: Pyridoxine-dependent epilepsy is an epileptic and developmental encephalopathy(DEE), usually neonatal onset, genetic etiology, autosomal recessive with characteristic patogenic variant in ALDH71A gene. Uncommon, variable incidence(1/20.000-1/783.000).
Approximately 75% have delayed psychomotor development and intellectual disability.
It does not respond to usual antiepileptic drugs.
Better response is seen with early diagnosis and treatment with pyridoxine.
Treatments associated with antiepileptics drugs, in partial response, arginine and a low lysine diet are described.
There are few reports of late diagnosis.
Our cases had a late diagnosis, with a good initial response to pyridoxine, requiring maintenance of antiepileptic drugs, but achieving improvement.
An exhaustive etiological study is recommended in epilepsies, which allows for adequate and early treatment, to achieve the best possible prognosis.

1411

"Alexa, how do you say "seizure": in Spanish?": investigating disparities in care of Spanish speaking children with Epilepsy and their barrier to medication adherence in Lexington, KY

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Purpose: Aim 1- To evaluate seizure frequency and barriers to antiseizure medications documentation in pediatric epilepsy patients. A Plan-Do-Study-Act (PDSA) method will be utilized.
Aim 2- To investigate if epilepsy patients and caregivers are queried by their neurologist or epileptologist about seizure frequency as well as barriers to medication adherence.
Aim 3- To investigate in the Spanish speaking epilepsy population if patients and caregivers are queried by their neurologist or epileptologist about seizure frequency. The survey will also enquire about barriers to medication adherence.
Method: For Aim 1- Retrospective chart review of seizure frequency and barriers to antiseizure medications documentation in pediatric epilepsy patients seen at the Child Neurology Turfland Epilepsy Clinic.
For Aim 2- Use a short survey with a quick response (QR) code about questions made by neurologist during encounter. The survey will be distributed through the Epilepsy Foundation of Kentucky and also made available to the Turfland Child Neurology Epilepsy Clinic.
For Aim 3- Use a short survey in Spanish with a QR code that will be distributed to various locations where children with epilepsy are being managed (UK ER, Turfland Child Neurology Clinic, and patients admitted to child neuro or followed by child neuro). Same questions than aim 2 but translated to Spanish.
Results: Data is being collected at the time of this abstract submission.
Conclusion: Pending :results being collected at the moment.

Pandemic Response

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Care of children with infantile epileptic spasms syndrome and applicability of telemedicine amidst the COVID 19 pandemic

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Purpose: To determine the impact of COVID-19 pandemic on the management of children with Infantile Epileptic Spasms Syndrome (IESS) and the role of telemedicine in facilitating health care during this tumultuous period.
Method: An ambispective, observational study was conducted at a tertiary-care centre in north India from Oct 2020 to June 2021. Caregivers of children with IESS were interviewed telephonically using a standard questionnaire (demographic details, information on health-seeking behavior, details of investigations, etiological work-up for IESS, anti-seizure medications prescribed, response to treatment and experience with telemedicine) and perusal of treatment records. The impact of pandemic on various parameters like diagnostic lag, treatment lag, response to treatment etc. were compared to a pre-pandemic cohort from the same study center.
Results: There was a significant increase in the diagnostic lag for children with IESS (p- value 0.039) during the pandemic. Hormonal therapy remained the preferred modality of treatment, with ACTH being the most commonly used medication, but the proportion of patients started on ACTH was lesser in comparison with the pre-pandemic cohort (53.8% vs. 62.9%). Response to treatment in study population was less than the pre-pandemic cohort (43.6% vs. 51.6%). Telemedicine was the most common modality of contact with the study center during the pandemic with around 80% of patients using it at least once. It was used for access to healthcare by parents regardless of educational status (p-value 0.18) with good satisfaction rates but given a choice parents continued to prefer physical consultations over tele-consultations.
Conclusion: COVID-19 pandemic and associated restrictions were associated with a significant change in the mode of healthcare delivery and access for children with IESS. Although telemedicine was fairly popular during the pandemic and had acceptable caregiver satisfaction scores, it remains second to physical consultations in terms of caregiver's preference.

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COVID-19 induced seizure in a tertiary medical center in Korea

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Purpose: Coronavirus disease 2019 (COVID-19) is a new human pathogen that causes respiratory syndrome. The major symptoms in infected people include fever, cough, pain, chills, and loss of smell or taste. Covid-19 can also cause neurological symptoms such as tingling in the hands and feet, vertigo, delirium, ischemic and hemorrhagic stroke, and seizures. The authors report a case series of COVID-19 induced seizures in a tertiary medical center in Korea.
Method: Electronic medical records of new-onset seizures in patients with COVID-19 patients.
Results: A total of 5,690 patients with confirmed COVID-19 were admitted to our hospital during the study period (2020 march to 2022 May). Out of these, 10 patients (0.17%) devel-

oped new-onset seizures during hospitalization. Patients' ages ranged from 29 to 83 years, and three of the ten patients were older than 60 years. Seven patients were men. Three patients were admitted to the intensive care unit (ICU). The duration from COVID-19 diagnosis to seizure onset ranged from 1 to 20 days. Seven patients were purposed magnetic resonance imaging (MRI) of the brain, and two of seven patients showed old hemorrhagic lesions. One patient had myoclonic status epilepticus, three patients suffered multiple seizures. Seven patients underwent EEG, two patients showed generalized slowing, one patient showed regional spike, one patient showed generalized polyspike and wave, and three patients showed normal EEG. All patients were receiving anticonvulsants or intravenous midazolam. Three patients died due to COVID-19 pneumonia or sepsis.
Conclusion: New-onset seizures are a rare complication of COVID-19 but may occur commonly in critically ill patients. It is still unclear how Covid-19 trigger the development of acute symptomatic seizure, direct brain invasion of SARS-CoV-2 may be related to the occurrence of seizures in COVID-19 patients with seizure. Further research is needed to probe and study the exact mechanism at a more molecular level.

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COVID-19 and epilepsy: clinical and neurophysiological aspects

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Purpose: to study clinical and neurophysiological changes after suffering COVID-19 in adult patients with epilepsy (PE).
Method: 50 PE were examined: 1st group - 25 PE had COVID-19 in the period from 2020 to 2022 and 2nd group - 25 PE didn't suffer COVID-19. All patients have clinical, EEG and psychometric examination with using scales and questionnaires: National Hospital Seizure Severity Scale (NHS-3), Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI), Spiegel's scale for assessing sleep, Multidimensional Fatigue Inventory (MFI-20), Mini-Mental State Examination (MMSE).
Results: The increase of the frequency of seizures was detected in 10 (40%) PE of the 1st group, in the 2nd group – in 2 (8%) patients (ϕ=0.0181; $p<0.05$). PE of the 1st group had a tendency to increase of frequency and severity of seizures: before COVID-19 SD=12.73 points, after COVID-19 SD=13.68 ($\chi 2$ =17.640, $p<0,01$). . Moderate depressive (ϕ=0.0458, $p<0.05$), more pronounced asthenia (ϕ=0.0352, $p<0.05$), decreased cognitive functions (ϕ=0.0378, $p<0.05$), moderate sleep disorders (ϕ=0.045, $p<0.05$) are more frequent in patients after COVID-19 compared to 2nd group. The EEG analysis before and after COVID 19 revealed diffuse EEG disorders and increase of synchronization of the cortex activity in PE of the 1st group.
Conclusion: The results of the study indicate a negative effect of COVID-19 on the bioelectric activity of the brain, frequency and severity of seizures and psychiatric disorders in PE and worsening of the course of epilepsy.

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Increased incidence of PNES during COVID-19 outbreak: impact of a pandemic

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Purpose: To assess the frequency of psychogenic nonepileptic seizures (PNES) during the COVID-19 outbreak in comparison to the pre-pandemic period and to recognize possible factors leading to aggravation.
Method: In this cross-sectional study conducted during the pandemic, adult patients attending the epilepsy clinic in a 3-month period with PNES documented by video-EEG/home video and followed up in a tertiary care epilepsy centre were selected and compared against baseline in the pre-pandemic period. Demographics, clinical features, frequency, and duration of PNES, presence of psychiatric comorbidity, as well as on anxiety (HADS-A items), depressive symptoms (HADS-D) and sleep quality were recorded.
Results: 26/1350 patients (65% female; age-26.7 years [4-68]) seen in epilepsy clinic during the pandemic lock down (3 months) were diagnosed to have PNES as compared to 49/ 7125 (71% female; age 28.9 years [5-63]) seen in the pre-pandemic period showing a 2.83 times elevation . 92 percent had an abnormal score (>11) on HADS-A or HADS-D. Patients with higher scores on HADS had recurrence of events during follow up at 6 months. There was strong correlation between higher anxiety scores ($p < 0.001$) and poor sleep quality ($p< 0.005$) with PNES aggravation. After regression analysis, higher anxiety scores were the strongest predictor of PNES increased frequency.
Conclusion: The frequency of PNES was 2.83 times high during the pandemic outbreak suggesting that such patients are vulnerable during stressors. Coexistent anxiety and depression increase the risk of seizure worsening.

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Seizure following COVID-19 vaccines in patients with epilepsy (PwE): a systematic review and meta-analysis

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Purpose: Seizure following immunization, especially in patients with epilepsy (PwE), has long been a concern, and seizure aggravation followed by COVID-19 vaccines is a serious issue for PwE. The immunization rate in PwE has been lower compared to same-age controls due to vaccine hesitancy and concerns about seizure control. We aimed to systematically review the seizure incidence in PwE after COVID-19 vaccination.
Method: Four search engines were searched from inception until September 15, 2022, and The Preferred Reporting Items for Systematic Reviews and Meta-Analyses followed. Random- and fixed-effect models using the logit transformation method were used for meta-analysis. Quality of the studies was evaluated by the Newcastle-Ottawa scale. Outcomes of interest included:(a) pooled proportion of increased seizure frequency; (b) pooled incidence rate of status epilepticus (SE) in PwE receiving COVID-19 vaccines.
Results: Of the 2207 studies identified, 18 met eligibility criteria, of which 15 entered the meta-analysis. The pooled proportion of increased seizure frequency (13 studies-3269 doses) was 5% (95CI: 4%-6%, I^2 =44%), further subcategorized into viral vector (7%, 95CI: 4%-12%, I^2 =1%), mRNA (6%, 95CI: 5%-8%, I^2 =2%), inactivated (4%, 95CI: 2%-7%, I^2 =67%) vaccines. The pooled incidence rate of the SE (13 studies-1864 doses) was 0.32% (95CI: 0.14%-0.71%, I^2 =0%), further subcategorized into the viral vector (0.00%, 95CI: 0.00%-1.00%, I^2 =0%), mRNA (0.11%, 95CI: 0.02%-0.79%, I^2 =0%), inactivated (0.00%, 95CI: 0.00%-1.00%, I^2 =0%) vaccines. No significant difference was observed between mRNA and viral vector vaccines (4 studies, 688 vs. 86 doses, respectively) regarding increased seizure frequency (OR: 0.92, 95CI: 0.34-2.51, p-value= 0.87).
Conclusion: The meta-analysis proposed a 5% increase in seizure frequency, no difference between mRNA and viral vector vaccines regarding increased seizure frequency, and a 0.32% incidence rate for SE following COVID-19 vaccination in PwE. This evidence is essential regarding the safety of COVID-19 vaccines in PwE.

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Pilot online pediatrics epilepsy referral network system(PERNs): from local to tertiary center in Thailand

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Purpose: Half of the epilepsy patients in Thailand had a large treatment gap. Drug resistant epilepsy patients need proper investigations and multidisciplinary teams approach which are mostly in tertiary centers. Neurological Institute of Thailand(NIT) aimed to develop the online, one-stop service referral system for children with drug resistant epilepsy from primary or secondary center to tertiary center care.
Method: The local physicians selected the children with difficult to treat-epilepsy and sent

their information; clinical course, Neuroimaging, electroencephalogram and others to our online platform. After real-time notification, the data were reviewed by the epileptologist in our center and concluded to proper investigations or management. Further clinical evaluation in detail can be made within the system. Nurse specialist will send back an appointment within 48 hours to the local doctor and the family, afterwards. Then, the patients admit doing the specific test or assigned management in only one visit. Multidisciplinary teams were approached as well.
Results: From January, 2019 to December, 2022, 58 patients were referred via PERNs. 35(60%) were appointed for 24 hours VIDEO-EEG monitoring, 30(51.7%) did MRI epilepsy protocol with anesthesia and 10(17.2%) went to an Epilepsy or Medical Cannabis Clinic. Mean number of visits/person/investigation were reduced from 3.4(regular referral system)to 1 visit(PERNs). Correspond to the non-medical cost and indirect medical cost/person/investigation were minimized from £454.9 to £133.7, respectively. The median waiting time was shortened from 122(82-161) days to 56(25-82)days (inpatients)and 22(7-35) days(outpatients), as well. Epilepsy surgery was done in 8(13.7%) children(median waiting time;85(72-130) days, 7(12%) were transferred back to primary centers.
Conclusion: This online system can shorten waiting time of investigations proceeding to epilepsy surgery in some cases. This also decreased the burden in time consuming and cost of multiple visits. The system is comfortable with primary physician to send the epilepsy patients to achieve the proper management in the Tertiary center.

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Online vs in-person seminars of the educational treatment programme for patients with epilepsy (MOSES) during the Covid-19 pandemic in Germany: a comparative analysis

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Purpose: To investigate how participants of innovative online MOSES courses evaluate the course compared to the participants of the established in-person MOSES courses.
Method: Four online (n= 32) and four in-person (n=38) training courses between March 2021 and March 2022 were evaluated with a standardized questionnaire covering the main aspects of the programme. Due to the explorative and qualitative character of the survey and the small sample size, the data were analysed with descriptive and nonparametric methods (Mann-Whitney U test, Fisher´s exact test).
Results: The two groups did not differ significantly with respect to age and gender (both

p>.20). On a scale from 1 (worst) to 5 (best), the different aspects of the programme have been rated high (median 3.0-5.0) in both groups. Overall, there were no significant (p>.10) differences between the training forms except for the chapter "psychosocial aspects", which was rated as significantly more important by the participants of the online course (p=.015). Regarding the course procedures, non-significant differences suggest that participants of the online course favoured to have further contact options with fellow participants (in-person 46% vs. online 55%) and assessed the way the trainers lead the course more varied (would expect the trainer to show "more restraint": in-person 3% vs. online 13%; "more leadership": in-person 5% vs. online 19%).
Conclusion: Participants of in-person as well as online MOSES courses assessed the programme predominantly positively, with no relevant differences between the two groups. However, explorative evaluation indicated some differences in the assessment of the trainers and the wish for further contact with the participants. This might be due to fewer contact opportunities during and the technical specificities of the online course. Further studies with a substantially increased sample size and evaluation tools specifically adapted to online courses are needed.

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Examining patient and provider engagement with an epilepsy self-management program targeting cognitive dysfunction during the COVID-19 pandemic

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Purpose: The COVID-19 pandemic disrupted healthcare access and self-management practices for people with epilepsy (PWE). The HOBSCOTCH (**HO**me **B**ased **S**elf-Management and **CO**gnitive **T**raining **CH**anges Lives) program has demonstrated in two RCTs improved QOL and cognitive function in PWE. A targeted effort was made to translate these evidence based program benefits from research to real world support by scaling program adoption and access, and examining provider and patient program engagement and subsequent QOL benefits experienced by PWE during the pandemic.
Method: HOBSCOTCH provider trainings and program delivery were transitioned to virtual (eighteen 8-hour trainings conducted 1/2020-12/2022) with implementation supported by the HOBSCOTCH Institute (HI). HOBSCOTCH availability was disseminated via websites, social media, community organizations and epilepsy centers. Referrals (clinician 56.8%, self- 27.2%, community 10.3%, family 5.4%) of PWE interested in the program were screened for participation..
Results: From 1/2020 through 12/2022, 102 clinicians and 65 community service providers completed training (89% increase compared to 1/2018 -12/2019). 372 PWE were pre-screened; >25 fold increase from 2018-2019. 35% (n=129) elected participation in HOBSCOTCH-3 RCT; 65% (n=243) chose general delivery (62% female; mean age 43.7; race, 71%

White, 5.4% Black, 4 % Asian; 75% non-Hispanic; 28% rural). Paired Pre/Post QOLIE-10 (n=96; 95% CI) demonstrated significant improvement ($p < 0.001$; Wilcoxon signed-rank test, pre (3.03 ± 0.07) and post (2.61 ± 0.08)). Satisfaction surveys (n=106), Likert scale (1-10), revealed program rating of 8.40 ± 0.22; 95%CI, very beneficial.
Conclusion: For telehealth implementation of epilepsy self-management (ESM) to be maximally effective it is critical to understand provider engagement and patient access. Real world HOBSCOTCH delivery during the pandemic crisis demonstrates a significant improvement in QOL comparable to improvement seen with prior RCTs. Broad dissemination of ESM programs requires the ability to scale real-world delivery to meet demand through investments in infrastructure and collaboration, and adaptation of outreach strategies to ensure equitable access.

Psychiatry

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Short video EEG in the detection of non-epileptic psychogenic seizures

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Purpose: To detect usefulness *of 5 hours Video EEG study in the detection on Psychogenic non Epileptic Seizures (PNES) in a region with limited access to long term Video EEG monitoring .*
Method: 68 consecutive patients with suspected PNES , were studied with a in -hospital 5 hours video EEG., from 2016 to 2022. All patients were studied with a non-sleep deprived 30 minutes basal study with 3 minutes hyperpnea (HV) and eyes closing photostimulation and later with two aleatory different suggestion tests : verbal suggestion during a new HV or subcutaneous placebo with oral suggestion.
Patients with negative study were sent to a complete 5 days continuous study in another medical center
All patients had complete anamnesis, general and neurologic examinations and psychiatric diagnosis were reviewed.
Percentage of positivity in detecting PNES , best suggestion test and clinical evolution is presented.
Results: From the first 68 patients (50 women and 18 men), two patients presented a PNES during non-suggestion study. In the rest, 42 patients disclosed a PNES , 8 epileptiform discharges with no seizure and 16 were normal. PNES were detected in 40 women and 2 men. Verbal suggestion during HV was slightly superior to subcutaneous in eliciting PNES.
In the 16 patients with negative study , a prolonged Video EEG showed 6 PNES , 8 epileptic events and 2 without abnormalities. From de 42 PNES patients followed with psychological/ psychiatric treatment , 1 patient experienced epileptic seizures, only 4 patients remains wih no PNES , 28 patients have decreased the number and intensity of events. Only 3 patients are kept with antiepileptic treatment besides all attempts to withdraw it.
Conclusion: In regions with small resources , a short Video EEG seems to be a good test to avoid massive transfer to tertiary centers.

No test seems better to elicit PNES.

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Suicide attempts in children and adolescents with functional dissociative seizures (FDS): an alert for awareness

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Purpose: Experiencing suicidal ideation or thoughts of self-harm occur in children and adolescents with FDS, though family members are frequently unaware. Therefore, these patients are at higher risk for suicide attempts. Thus, we assessed the frequency and predictors of suicide attempts in this sample.
Method: In this unicentric and retrospective study, we reviewed medical files of children and adolescents (6-17 years) with FDS. A multidisciplinary team evaluated all participants during their diagnostic admission. Simple linear regression analysis was performed for prediction analysis, with suicide attempts as the dependent variable and other factors as independent variables (demographics [sex, age], FDS-factors [age onset; diagnosis delay; co-existing epilepsy; numbers of events; time until the first event during monitoring; semiology], predisposing factors to FDS, perpetuating elements of FDS; the presence of neurology and psychiatry diagnosis; family history of epilepsy and psychiatry conditions).
Results: Fifty-three consecutive patients (32 girls [60.4%] with a median age of 13.0 years and mean age of 12.8 years [SD=3.2]) were consecutively enrolled in this study. Six patients had a previous history of suicide attempts (11.32%). Family members were unaware of suicidal thoughts in all patients. The presence of stressors as a possible trigger to FDS predicted suicide attempts (R=0.344; R2=0.119; adjusted R2=0.101; standard error of the estimate=0.309; standard coefficients B=-0.344; t=-2.567; p=0.013). Twenty-eight patients/families identified a potential stress factor, such as environmental triggers (52.83%), namely: bullying (n=4; 14.285%), abuse (n=4; 14.285%), academic issues (n=13; 46.428%), family discord (n=7; 25%), both school and family stressors (n=1; 3.571%).
Conclusion: Children with FDS were at higher risk for suicide attempts. Environmental stressors were a predictor of suicide attempts. Therefore, it is mandatory to alert parents and caregivers to suicidal behavior in children and adolescents with FDS.

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Clinical characteristics of patients with refractory non-epileptic seizures

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Purpose: The incidence of non-epileptic seizures (NES) is estimated to be between

1-35/100,000. The prognosis and outcomes for these patients are variable, with many studies quoting less chance of event freedom than a diagnosis of epilepsy. The purpose of this study was to examine the characteristics of population of patients with refractory NES at a tertiary epilepsy referral centre.
Method: A retrospective chart review was conducted on all patients diagnosed with refractory NES using video telemetry in an epilepsy monitoring unit over a 6 year period. The definition of refractory NES was taken to be persistence of NES at least one year post diagnosis. Data pertaining to predisposing, provoking and precipitating factors was collected on each patient.
Results: 24 cases of refractory NES were identified (28% of all NES diagnoses) with a 7:1 female to male ratio. Co-morbid active epilepsy or primary mental health disease was present in at least one third of cases. Only 23% achieved third level education, with 21% in school at the time of diagnosis. Adverse psychosocial events were encountered in 87% of cases, making this the most commonly encountered risk factor in our cohort. A clearly identifiable precipitant was identified in 46%.
Conclusion: This study provides a detailed analysis of a population of patients with refractory NES and provides some useful insights into prognostication in such a disabling condition.

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Interictal psychosis in patients with epilepsy – what are the risk factors?

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Purpose: Epilepsy is a chronic disease of the central nervous system, and the most common neurological disease globally, affecting people of all ages. People diagnosed with epilepsy have been noticed to be particularly linked to certain psychiatric disorders, episodic psychoses, one of which is called interictal psychosis (IIP) and which is the topic this systematic review will focus on. The objectives of this systematic review were to find out whether there are certain characteristics of the epilepsy syndromes or treatments that predispose to the occurrence of IIP and general psychopathologies that are commonly noticed in epileptic patients.
Method: Embase, PubMed, Web of Science and Scopus were searched for relevant studies published from 2018-2022. SPIDER criteria (Sample, Phenomenon of Interest, Design, Evaluation, Research type) were used to determine the inclusion criteria. 111 studies were screened for suitability in English or German and 7 were included in this review.
Results: All included studies experienced the occurrence of IIP with the introduction of antiseizure medications (ASMs), with Lacosamide, Levetiracetam, Carbamazepine and Sodium Valproate or valproic acid being the ones used the most. When looking at the studies' results, it could be noticed that focal epilepsies were more likely to be associated with IIP than generalized epilepsies. Another aspect mentioned in one study was that the early onset of epilepsy and therefore the longer duration might play a role in the occurrence of IIP.

Conclusion: Overall, most studies showed that IIP occurs in many patients with epilepsy and that ASMs play a particular role in the development of such. However, ASMs are essential in the treatment of epileptic seizures meaning that particular thoughts need to be made about how the duration and dosage of ASMs may limit seizures as fast as possible and don't lead to the development of IIP.

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Psychogenic non-epileptic seizures in patients with idiopathic generalised epilepsy: A single-centre video-electroencephalography retrospective study

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Purpose: Epilepsy and psychogenic non-epileptic seizures (PNES) commonly co-occur, presenting significant diagnostic and therapeutic challenges. This phenomenon is more commonly described in patients with focal epilepsy compared to those with idiopathic generalised epilepsy (IGE). Here, we evaluate the relationship between PNES and IGE diagnosed by video-electroencephalography (vEEG) at our epilepsy centre.
Method: We performed a retrospective study of 116 patients with potential IGE referred for vEEG investigation between 2007 and 2022. Baseline clinical data were obtained from our epilepsy Electronic Patient Record. Patients were included if they had a confirmed diagnosis of IGE (either historical or by vEEG) and PNES recorded during the vEEG admission.
Results: We identified 29 patients with IGE and co-morbid PNES captured during the vEEG admission. Twenty-seven patients were female (93.1%). Mean age was 26.2 years (range 16-45 years). The mean age of seizure onset was 13.6 years (range 1-29 years). The mean length of admission was six days (range 2-14 days). Generalised tonic-clonic seizures (GTCS) were reported by 89.6% of patients, absence seizures by 65.5% and myoclonus by 50%. The median number of current antiseizure medications (ASM) was two (range 0-5).
Inter-ictal abnormalities were seen in 28 patients (96.5%). Generalised seizures were recorded in fifteen patients (51.7%), with a mean of 2.13 seizures per admission (range 0-15). GTCS and absence seizures were seen in five patients, myoclonus in four, and eyelid myoclonia in two. Most patients had more PNES recorded than epileptic seizures (93.1%), with a mean of 6.28 PNES per admission (range 1-24). Common PNES semiology included akinetic-unresponsive presentations (18/29, 62%) and hypermotor events (15/29, 51.7%).
Conclusion: Co-morbid PNES was common in patients with IGE referred for vEEG. PNES may be mistaken for GTCS or absence seizures given the similar semiologies, leading to "pseudo-resistance". vEEG is the gold-standard investigation to differentiate epileptic seizures from PNES.

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Parents' experiences of sleep, sleep problems and their management in children with epilepsy

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Purpose: Sleep problems in children with epilepsy are common. Little is known about parents' experiences and perspectives of managing sleep and any sleep problems in their child. To provide the most appropriate services' provision, it is essential that the lived experience of parents of this patient group and the issues and problems that they face in managing their child's sleep is understood. The current study aimed to identify parents' experiences of managing sleep and any sleep problems in children with epilepsy.
Method: Nine mothers of children with epilepsy took part in semi-structured interviews. Thematic analysis was conducted on the data and themes identified that represented parents' experiences around their child's sleep and available support.
Results: Seven themes represented mothers' experiences of managing their child's sleep and any associated problems, including the longstanding challenging nature of child sleep issues, the broad range of management strategies they had tried, challenges related to managing sleep over time, the link between sleep and seizures, the negative impact of poor sleep on daytime functioning, role of antiseizure medication and maternal concerns about child sleep. One theme represented the perceived lack of information, help and support available.
Conclusion: Findings highlighted parents had ongoing and diverse needs of support with sleep for their children with epilepsy. There is a need to address this unmet need.

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Developing an online behaviourally based sleep intervention for parents of children with epilepsy for use in a large multi-site UK based randomised control trial

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Purpose: Common types of sleep problems experienced by children with epilepsy (CWE) are the same as those experienced by typically developing children and other childhood neurode-

velopmental populations. Behavioural sleep interventions (BSIs) have a strong evidence base, but lack evidence to specifically support their use in CWE. The objective of the current study was to develop an online BSI for parents of CWE to use.
Method: Phase 1. Developing the online sleep intervention. Ten mothers and three children with epilepsy took part in semi-structured patient and public engagement interviews. Thematic analysis was undertaken to identify key content or delivery adaptations to standard BSI, which would be required to best meet the needs of this participant group. This information was used to guide our decisions about content and functionality. Phase 2. Evaluating the functionality of the online BSI. Six mothers evaluated the intervention until approval was reached.
Results: Phase 1. Two existing evidence-based BSIs were identified as the foundation of content. This material was amended to i. include specific content requested by parents of children with epilepsy, such as including information about the relationships between sleep and seizures, representing other parents' experiences and addressing parental and child worries about sleep and ii. address specific delivery requests such as ensuring advice was practical but non-prescriptive and provided personalised information and advice. Phase 2. Parents of CWE explored the intervention website and reported it to be appropriate in terms of content and functionality. All parents said they would recommend the intervention to other parents of children with epilepsy (the key approval metric).
Conclusion: The online BSI is currently being evaluated in a large multi-site randomised control trial. It is hoped that the use of evidence based strategies with acknowledgement of specific considerations for this patient group will contribute to its usefulness and efficacy.

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Idiopathic generalized epilepsy: psychiatric symptoms

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Purpose: To describe the psychiatric symptoms of patients with idiopathic generalized genetic epilepsy in general and subgroups in our healthcare center.
Method: The database of patients from our institution from 2019 to 2022 was retrospectively reviewed, including patients diagnosed with idiopathic genetic epilepsy.
Results: We obtained a total of 231 patients. The mean age was 13 years, 54.54% male, and the mean age of the first crisis was 12 years (range 7-35 years). The most frequent diagnosis was juvenile myoclonic epilepsy, 108 patients (54.62% men) 10 women and 21 men presented associated psychiatric symptoms, aggressiveness 1 (3.23%), depressive symptoms 14 (45.16%), anxiety symptoms 13 (41.94%), unspecific substance abuse 2 (6.45%), eating disorders 1 (3.23%). Generalized epilepsy with only generalized tonic-clonic seizures, 76 patients (55% men), 6 women and 2 men presented associated neuropsychiatric symptoms, anxiety

symptoms 3 (37.5%) depressive symptoms 2 (25%), unspecific substance abuse 2 (25%) and aggressiveness 1 (12.5%). Of 28 patients with childhood absences, an 8-year-old girl presented psychosis as an isolated neuropsychiatric symptom. The juvenile absence epilepsy group consisted of 19 patients without associated neuropsychiatric symptoms.
Conclusion: In our study it was observed that in 3 of the 4 groups of idiopathic generalized epilepsy, there were associated neuropsychiatric symptoms (17.32%), both anxiety and depressive symptoms being the most frequent (40% each), 17 women (42.5%) and 23 men (57.5%).

Social Issues

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Perception of family support in patients with epilepsy

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Purpose: To evaluate the perception of family support in patients with epilepsy (PWEs) and correlate it with quality of life (QoL) and clinical variables. To compare the perception of family support between a group of PWEs and a control group (CG) of individuals without chronic diseases.
Method: The Perceived Family Support Inventory (PFSI) was administered to 120 PWEs and 26 individuals from the CG. PFSI data were related to clinical variables and scores from the Quality of Life in Epilepsy Inventory-31 (QOLIE-31) and the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E).
Results: PWEs age was 49.7±16.8 years and length of epilepsy was 20.5±15.8 years.
There was a difference between PWEs and CG individuals in the total PFSI score (T test, 65.8±14.1 vs 59.3±17.4;p=0.043) and in the conscious affective dimension (32.1±8.9 vs 25.8±10.8;p=0.002). There was a significant correlation between the total scores of the QOLIE-31 and the total scores of the PFSI (Pearson's correlation, r=193;p=0.028) and the family adaptation dimension of the PFSI (r=285;p=0.001). There was correlation between the social support dimension of the QOLIE-31 and the family adaptation dimension of the PFSI (r=177;p=0.046). A greater perception in the affective-conscious dimension occurred in married PWEs (T test, 33.5±9.1 vs 30.1±8.3;p=0.035) and in those with better seizure control (28.2±11.9 vs 33.4±7.3;p=0.027). The presence of depression associated with a lower perception of family adaptation.
Conclusion: A good perception of family support was found in the PWEs. Aspects of family support were associated with demographic aspects, epilepsy variables, and the perception of better perception of QoL. Family relationships can play an essential role assisting self-care

behaviors and maintaining QoL in epilepsy. Family behaviors of poor adjustment to epilepsy and negative behaviors can be characterized by overprotection or limitations in activities of daily living of PWEs.

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Attitudes of Bulgarian patients with epilepsy to COVID-19 vaccination

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Purpose: To assess the COVID-19 vaccination coverage, vaccination willingness, the factors associated with vaccination hesitancy and the sources of information of Bulgarian patients with epilepsy.
Method: We included 103 (53 women) Bulgarian patients with epilepsy. They completed a questionnaire about socio-demographic and epilepsy-related characteristics, history of COVID-19 disease and COVID-19 vaccination, attitudes towards vaccines, sources of information about COVID-19 disease and vaccination.
Results: One third of the participants were vaccinated against COVID-19. The vaccination was associated with higher seizure severity $P < 0.0015$ ($\chi2 = 5.95$) and consultations with medical staff about vaccines $P < 0.05$ ($\chi2 = 7.58$). All of the vaccinated participants confirmed that vaccines are useful for most people without causing long-term adverse events or complications ($P < 0.001$, $\chi2 = 44.29$), that vaccination is the only way to gain immunity apart from acquiring the disease itself ($P < 0.001$, $\chi2 = 23.97$) and that vaccination is also useful in healthy people with no existing disease ($P < 0.001$, $\chi2 = 83.29$). After detailed explanations about the efficacy and safety of COVID-19 vaccines about a half of the non-vaccinated participants consented to be vaccinated in the future. The rest of 35 (50.7%) patients dissented to vaccinate due to various reasons: fear of long-term adverse events, inefficacy, infection, mistrust in vaccines and/or any experimental methods for treatment and prevention. Some of them (14.3%) felt themselves protected after suffering from the disease.
Conclusion: Hesitancy and erroneous beliefs about the efficacy and safety of COVID-19 vaccination are frequent among Bulgarian patients with epilepsy. The results from our study suggest the need of a more active and directed to patients with epilepsy approach with provision of reliable information to the medical staff and general population.

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An integrated to approach to provision of community care pathway for epilepsy care to vulnerable populations in an urban setting - the homeless person with epilepsy

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Purpose: **Background:** Epilepsy among homeless person poses a serious health problem

- Higher prevalence rates of epilepsy 8 times the rest of population
- Homeless epilepsy patients have a high degrees of contact with the Emergency Department > 500 admissions per year with epilepsy
- Contributes to social exclusion and access to specialist care
- Most are men 40-50
- Co-morbid addiction
- risk of death is 5/100 compared to 1/1000
- Majority (78%) of those who die in a seizure have no anti-epileptic drugs in their system

Aim and objectives**:** To reduce in the dependence of patients with severe epilepsy on the ED by intervening earlier in the patient journey to prevent ED presentations in this patient group
Method: This project is provides an integrated approach to inclusion health with an Advanced Nurse Practitioner in Epilepsy working with dedicated Inclusion Health Primary Care Team and uses a variety of techniques including virtual outreach, a physical homeless mobile epilepsy clinic in a Dublin City Center locations, intelligent e-support for GPs and an integrated electronic record to deliver a Integrated Care Pathway in the Community for vulnerable patient populations.
Results: An evaluation will measure ED visits and look at other critical outcomes as measures to patient centred-care.
A point of care electronic record created with the national epilepsy electronic record allowing for cross-referencing hospital numbers from ED presentations or HIPE data in those admitted with the epilepsy EPR providing detailed monitoring data.
Conclusion: The potential for scaling up and replicating this inclusion health project around the county is high especially in urban centres with high rates of homelessness and residential centres.

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Othello's epilepsy

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Purpose: Othello is one of the most popular plays in Shakespeare's canon. Othello has a seizure in the fourth act of the play, and a character describes his fit as "an epilepsy". Othello is a

fictional character, and Shakespeare's source, a short story by Cinthio, makes no reference to this illness. This work asks what purpose Shakespeare's insertion of Othello's epilepsy serves in the narrative and drama of the play. It then discusses how this portrayal, in a work still performed regularly and studied in schools and universities, reflects modern views of epilepsy and its relationship with psychological and other factors.
Method: A review of Shakespeare's play, and of the literature on this topic, with some additional observations.
Results: There are several possible reasons for Shakespeare's invention of Othello's epilepsy. He may be influenced by historical and mythical precedent, in the epilepsy of broadly similar characters such as Julius Caesar (the subject of an earlier Shakespeare play) or even the myth of Hercules. There are hints that his epilepsy may be post-traumatic. Shakespeare may have regarded a seizure as a marker of Othello's psychological deterioration from hero to jealous lover. Alternatively, he may have regarded epilepsy as a possible contributor to Othello's confusion. Finally, medical understanding of epilepsy was less advanced, and magical theories surrounding epilepsy and demons or spirits would have been more current, so Shakespeare and his audience may have regarded a seizure as a form of curse.
Conclusion: There are multiple theories to explain Shakespeare's decision that his fictional character, Othello, should have a seizure. Othello is a popular play to this day, and people with epilepsy and their families will continue to be exposed to such portrayals of epilepsy. Such context helps physicians to understand current attitudes to epilepsy.

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Experiences and impact of public involvement in epilepsy awareness through national epilepsy programme before and during the COVID-19 pandemic

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Purpose: National Epilepsy Coordination Committee (NECC), formed in 2010 to connect epilepsy stakeholders in Kenya, improve knowledge and care and implement international resolutions on epilepsy. Principal goal for epilepsy awareness programs by NECC is to combat stigma, increase access to care and improve quality of life. The impact of awareness, including during the COVID-19 are not documented.
Method: We engage local and national departments of health to design strategies for epilepsy awareness and increasing care in Kenya. Since 2010 we organized bimonthly meetings with stakeholders and engaged community radios on epilepsy talk. We trained primary health care workers and Community Health Volunteers to educate people in native language. Utilized the social media to post educative videos targeting youth. Involved community in fitness walks inclusive of people with Epilepsy.

Results: Before COVID-19 pandemic we held 12 policy meetings on future of epilepsy in Kenya, partnered with 19 county governments to create awareness and training. Mass media sensitization reached 10 million people nationally and developed two versions of guidelines for management of epilepsy. Members participated in international epilepsy initiatives e.g with ILAE and IBE. From 2020 to 2021, activities were affected by the pandemic, e.g., community sensitization closed, Slow uptake of online training by Health care workers and Community Health volunteers, reduced funding. We resorted to innovative ways to raise awareness nationally e.g. community local radio stations and social media platforms, which reached 6.5 million people nationally. We engaged more epilepsy stakeholders to join NECC from 17 to 23 members, incorporated more sponsors from Corporate companies.
Conclusion: National epilepsy partnership with international organizations can be effective in creating epilepsy awareness and improving care, but requires enthusiastic members, financial support and good political will. Sustained support is needed to formally evaluate effectiveness of these programmes and set up similar national programmes in other countries in Africa.

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Seizure first aid for people with epilepsy: opinions and knowledge of caregivers and healthcare professionals

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Purpose: We investigated the opinions and knowledge of the caregivers of people with epilepsy (PWE) and the related healthcare professionals (i.e., nurses and physicians) in Iran about first aid measures for helping a person experiencing a seizure.
Method: In this exploratory and descriptive study, we surveyed the caregivers of all PWE admitted to the epilepsy monitoring unit at Namazi Hospital, Shiraz, Iran, in May 2022. We also surveyed all the nurses at this hospital. A similar survey was distributed in the WhatsApp groups of the neurology, pediatrics, internal medicine, family physician, psychiatry, and neurosurgery physicians working at places affiliated with Shiraz University of Medical Sciences, Shiraz, Iran.
Results: In total, 583 nurses, 70 physicians, and 133 caregivers participated in this study. On most questions, more caregivers provided inappropriate responses than nurses and physicians (e.g., not timing the seizure; not loosening the clothes around the neck; not rolling the patient onto the side if unconscious). On two questions, more caregivers provided appropriate responses than nurses and physicians (i.e., not putting something into the mouth; not always calling for emergency medical services).
Conclusion: While some actions may help prevent or reduce the chance of harmful conse-

quences of epileptic seizures, many caregivers of PWE and healthcare professionals do not apply appropriate measures to help a patient experiencing a seizure. The scientific community should develop standardized seizure first aid training programs for the general public and healthcare professionals alike.
[Published: September 15, 2022 in Seizure - European Journal of Epilepsy DOI: https://doi.org/10.1016/j.seizure.2022.09.007]

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Epilepsy care pathways for patients experiencing homelessness in the Dublin inner city: a service evaluation post-quality improvement project

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Purpose: Patients experiencing homelessness are vulnerable to poor health outcomes, experiencing higher rates of epilepsy with greater morbidity compared to the settled population. Our 2020 project showed that implementation of a dedicated care pathway led to significant improvement in establishing a diagnosis and communicating a management plan to primary care providers.
The aim of this study was to follow up on the clinical outcomes of the original 2020 patient cohort, and to review the current state of the care pathway.
Method: A retrospective review of the 2020 group (n=46) was conducted using our hospital EPR. Information gathered included: whether the patient was deceased and cause of death, number of seizure-related ED presentations, number of patient-service contacts and nature of contact, whether those without a diagnosis of epilepsy had been subsequently diagnosed, and whether treatment had been changed. Further data collection will compare a new cohort of 2023 referrals with the original group.
Results: Of the original cohort: 4 (8.7%) were deceased, 2 (4.3%) of these deaths were seizure-related. 19/46 patients (41.3%) presented to ED with seizure at least once since referral. 18/46 patients (39.1%) had no further interaction with our service, 3 of whom were diagnosed with epilepsy.17/46 patients (37%) did not have a diagnosis of epilepsy; none were subsequently diagnosed. 12/46 patients (26.1%) had changes made to their treatment in the interim. Data collection regarding referrals from January 2023 onwards is ongoing. This will allow for comparison with our original cohort, and review of the standard of care.
Conclusion: This project underscores the need for specialised pathways in the management of seizures in patients experiencing homelessness. This approach could be applied in other centres, across multiple chronic disease models in this cohort. We will continue to evaluate the efficacy of our pathway, to ensure that this group of patients receive appropriate specialist assessment.

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Factors associated with the internalized stigma in people with epilepsy in Medan, Indonesia

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Purpose: Stigma towards epilepsy is associated with a negative self-concept and has a negative impact on people with epilepsy (PWE) and their families, especially in low to middle-income countries in which the large majority of PWE live. This study aimed to evaluate stigma and determine the factors associated with internalized stigma in people with epilepsy.
Method: This was a descriptive-analytical cross-sectional study carried out among patients attending the neurology outpatient clinic of two university teaching hospitals in Medan North Sumatra Indonesia. Participants were recruited using a non-random consecutive sampling method. We included illiterate patients with generalized and focal epilepsy older than 18 years who could communicate fluently in Bahasa Indonesia and had no psychiatric comorbidities. The Internalized Stigma of Epilepsy has been validated in Bahasa Indonesia and was used to evaluate the stigma. It consists of five subscales measuring alienation, stereotype endorsement, perceived discrimination, social withdrawal, and stigma resistance. Each item has four response options scored using a Likert scale from 1 to 4.
Results: At the moment we are still collecting the data until August 2023.
Conclusion: This is still an ongoing study.

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Implications for driving based on the conditional risk of seizures after ischemic stroke

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Purpose: The risk of unprovoked seizures following ischemic stroke may impact the ability to drive. We evaluated whether a personalized prediction of seizure risk using a novel prognostic model ($SeLECT_{2.0}$) may support decisions on the ability to drive.
Method: We analyzed data from a multicenter study of post-stroke seizures including 4,452 adults from 9 international cohorts with neuroimaging-confirmed acute ischemic stroke and without a past history of seizures (mean age 73 years, 56% male). We calculated the chance of an occurrence of a seizure in the next year (COSY) using the SeLECT2.0 model. We considered a COSY < 20% safe for private driving and < 2% for professional driving, in line with commonly-used regulation in many countries.
Results: Seizure risks were mainly affected by an individual's baseline characteristics captured using the $SeLECT_{2.0}$ score and, to a lesser extent, by the seizure-free interval (SFI) following stroke. Stroke survivors without acute symptomatic seizures ($SeLECT_{2.0}$ between 0 to 6 points) have a low COSY at baseline (range 0.7 to 9%), thus not requiring a SFI to reach a low COSY. In those with acute symptomatic seizures ($SeLECT_{2.0}$ between 3 to 13 points) COSY following a 3-month SFI ranged from 3% to 93%, thus indicating a large variability of individual risk in this population. Those with acute symptomatic status epilepticus ($SeLECT_{2.0}$ between 7 to 13 points) had the highest risk of seizures (range 16 to 93% following a 3-month SFI).
Conclusion: A personalized approach using prognostic models may be more appropriate than relying on generic seizure-free intervals to guide decisions on driving after stroke. Our results provide practical charts that will help determine a stroke survivor's risk of seizures and the appropriate SFI to meet driving regulations.

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Seras-EEG trial: technical correlation between conventional EEG recording and the mjn-SERAS device for subsequent analysis by an artificial intelligence-based system for seizure early detection

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Purpose: mjn-SERAS is an earpiece shaped as a hearing-aid device, which continuously records the electrical brain activity. It uses an algorithm artificial intelligence (AI)-based system for early detection of seizures. Seras-EEG trial study the correlation between conventional EEG records and mjn-SERAS to identify preictal and interictal segments in drug-resistant epilepsy patients.
Method: We studied a group of 16 patients with drug-resistant focal epilepsy and 14 controls. Both groups used mjn-SERAS, that records two channels in the external auditory canal and simultaneously performed EEG 24-channel recordings using the 10-20 system. Subsequently

we extracted data from channels F8-T4 or F7-T3, according to the laterality of the epileptic focus. We analyzed the average correlation (AC) between the two types of records, with and without artefact removal, filtered records (FR), comparing inter-subject and subjects recordings (SR), as well between ictal and interictal periods in epilepsy patients.
Results: We obtained an AC of 88,2% (CI95% 86.6 - 89.8) in no FR; 90,2% (CI95% 89.0 - 91.4) in FR and 90,1% (CI95% 88.1 - 92.1) in SR. In cases group, an AC of 89,3% (CI95% 87.6 - 91.0) in FR and 89,5% (CI95% 86.6 - 92.4) in SR; controls results included 91,1% (CI95% 89.2 - 93.0) in FR and 90,7% (CI95% 88.3 - 93.1) in SR. Results distributed by ictal periods with AC of 88,0% (CI95% 83.3 - 92.7) and interictal periods of 89,4% (CI95% 87.6 - 91.3). The results support an adequate correlation between the information recorded with both methods.
Conclusion: Seras-EEG trial provides technical support for use of the mjn-SERAS to record EEG signal compared to the gold standard. A prospective, multicentre, pilot clinical trial is currently in progress to evaluate the mjn-SERAS in real life to anticipate seizures and describe improvements in different areas of personal development of epilepsy patients. **Acknowledgment:** International multidisciplinar consortium funded by EIT

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National Epilepsy Regional Clinical Cooperation System Project in Japan

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Purpose: Epilepsy care in Japan has been provided by departments such as pediatrics, psychiatry, neurology and neurosurgery, resulting in a situation where not only patients but also medical institutions do not know which medical institution provides specialized epilepsy care. Patients with epilepsy are not always linked to specialized medical care in the community, as systems for providing information and education on epilepsy care to general physicians are not yet in place.
Method: In 2018, the Ministry of Health, Labour and Welfare launched the National Epilepsy Control Regional Medical Care Coordination and Development System Project. Each prefecture selects a medical institution to provide measures against epilepsy and designates one of the medical institutions specializing in the treatment of epilepsy as an epilepsy treatment center.
Results: The duties of the epilepsy treatment centers include: specialized consultation support and treatment for epilepsy patients and their families; advice and guidance to medical institutions in the area; cooperation and coordination with mental health and welfare centers, health centers, municipalities, welfare offices and public employment security offices; training for medical personnel, staff of relevant institutions, epilepsy patients and their families; and public awareness raising activities for epilepsy patients and their families, local residents and other people with epilepsy.
Conclusion: The epilepsy medical support coordinator plays an important role in this epilepsy support project. The requirements for coordinators are that they have understanding and enthusiasm for the welfare of persons with mental disabilities, have the ability to provide appro-

priate consultation and assistance to epilepsy patients and their families, and have national qualifications in medical and welfare matters. A coordinator training and certification system was launched in 2020 to educate and train coordinators. In addition, to expand the scope of epilepsy treatment, medical facilities providing epilepsy treatment nationwide are listed on the website of the National Epilepsy Support Network.

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Assessment of impact of racial demographics on bias in machine learning models for IED Detection

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Purpose: Machine learning algorithms are transforming the interpretation of EEG. However, implicit bias in machine learning algorithms is often overlooked. This bias can be the result of lack of diversity in training and testing data, inequitable data collection, or other factors that result in poor generalizability and healthcare inequity. Beacon Biosignals develops machine learning models to support advanced analysis of EEG, and harnesses diverse datasets from the Beacon Datastore™ to train models for maximum generalizability. Here we examine the effects of race on the performance of a deep learning-based interictal epileptiform discharge (IED) algorithm to ensure equivalent performance across demographics.
Method: Beacon's IED detection algorithm was originally trained on clinical EEG data from 6,471 subjects (original model). As determined by the medical record, 73% of subjects were categorized Caucasian and no other demographic accounted for more than 10%. To determine the impact of this demographic skew, we retrained the IED detection model using Caucasian subject data (experimental model) and tested on all demographics. A decrease in performance on non-Caucasian subjects would indicate underlying model bias, necessitating correction to avoid perpetuating health care inequities.
Results: An analysis of the experimental model demonstrated specificity of 81% and 85% on Caucasian and non-Caucasian data, respectively. Sensitivity was 85% and 84%, respectively. Positive and negative predictive values and AUCROCs (area under ROC curves) were equivalent.
Conclusion: Examining bias in machine learning models is critical for generalization and equitable performance across diverse patients. Although fundamental neural processes are identical across races, biases in data collection could impact IED algorithm performance. Here, we found no evidence of experimental model bias favoring Caucasian subjects – but had insufficient data to assess for bias against any specific racial group. We propose future work to include model validation using additional data sets and data re-sampling to achieve more equitable distributions.

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An updated examination of transport use during driving restriction in patients with epilepsy in Ireland

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Purpose: Driving restrictions have a significant impact on patients with epilepsy and their families exacerbated by lack of access to reliable transport when personal car use is restricted. Patients' options for mobility are significantly curtailed without personal car access, particularly in a patient cohort which includes people living rurally. The goal of this ongoing study is to examine this impact on an Irish tertiary hospital cohort.
Method: Patients were recruited through the Beaumont Hospital neurology service during the one-year period of driving restriction implemented following an epileptic seizure. Patients were subsequently contacted by phone and interviewed using a standardised proforma.
Results: Our analysis includes 23 patients (female 65%, mean age: 45.8 years) interviewed during a period of driving restriction. Among this cohort, 48% (n=11) of patients had not previously been restricted from driving. Prior to the onset of driving restriction, the majority of patients (96%, n=22) reported a personal car as their primary mode of transport. The single additional patient (n=1) using public transport. Primary reasons for transport use included work (44%), personal (43%) and children (13%). All driving patients (n=22) were personal car (group 1) drivers with one patient working as a taxi driver. During restriction, 61% (n=14) continued to primarily use a car driven by a friend or family member. Three patients (13%) switched from personal car use to public transport with the majority reporting at least partial access to public transport (83%, n=19).
Conclusion: A personal car is the primary mode of transport in this cohort both before and after driving restriction. Despite patients reporting access to public transport, its use remained limited with continued car use albeit as a passenger. This highlights the limited options considered by patients for transport and the potential burden on others in providing transport for patients.

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survey about multidisciplinary consultations "work and epilepsies" in France

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Purpose: Approximately 50 million people worldwide are affected by epilepsy. Employers' stigmas hinder hiring and lasting employment of patients with epilepsy. Multidisciplinary consultations are a medical tool for neurologists and occupational physicians to provide advice to those in these situations. In France however, these initiatives aren't standardized. The aim of

this study is to initiate a survey on a national interviewing professionals.
Method: From June to October 2022, a pool of specialists working in the field of epilepsy and occupational medicine, and working group from the French National Authority for Health, were contacted by email to know if they took part in multidisciplinary consultations. These let us identify institutions to interview.
Results: 32 professionals responded and 16 centers offering multidisciplinary consultations were identified. Neurologists (47%) and occupational physicians (41%) were the majority of respondents. The centers pioneering in work and epilepsy consultations more than 10 years ago were: Lyon, Lille, Rennes and Paris Sainte-Anne. Despite the lack of standardization, some recurring aspects were found: i) Quarterly consultations take place mainly in the "epileptology" departments, ii) Sessions last between 45-90 minutes, ii) Up to five patients are seen. Throughout the study, several areas for improvement were highlighted: i) Need of exchange and networking between centers ii) Insufficient territorial coverage iii) Absence of official label and support from Health Authorities.
Conclusion: Exchange of practices about Multidisciplinary consultations in France: Work and Epilepsies is essential to help physicians and patients, whose employment is concerned. The creation of French (CRéER) and European centers (EPICARE) will make it possible to define guidelines and provide a platform to improve and evaluate practices.

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Health science students' knowledge about epilepsy

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Purpose: Analyse and compare knowledge about epilepsy between medical and non-medical students of Lithuanian University of Health Sciences.
Method: Students participated in an online survey in which they had to choose correct answers about epilepsy. The survey was sent through the official email system of LUHS in 2022. It was sent to 600 and answered by 228 (38.0%) students - 130 (57.0%) medical and 98 (43.0%) non-medical students (of odontology, nursing, pharmacy, veterinary, etc.). Medical and non-medical student groups did not differ by gender and age ($p>0.05$).
Results: The correct answer that epilepsy is a neurological disease did not differ ($p>0.05$) between medical (116 (89.2%) and non-medical students (81 (82.7%).
Students who correctly chose all 5 epilepsy causes (head trauma, genetics, brain tumor, birth trauma, stroke) given in the survey did not differ ($p>0.05$) between the two groups; however, more medical 102 (78.5%) compared to 63 (64.3%) non-medical students chose head injury (respectively 102 (78,5%) and 63 (64.3%), ($p<0.05$) and brain tumor (respectively 85 (65.4%) and 49 (50.0%) as the correct answers ($p<0.05$).
All 4 epileptic seizure symptoms given in the survey were chosen correctly by 69 (53.1%) medical and only by 35 (35.7%) non-medical students ($p<0.05$). Moreover, 118 (90.8%)

medical students chose postictal confusion as the correct answer compared to 77 (78.6%) non-medical students and an episode of memory loss (respectively 89 (68.5%) and 54 (55.1%) ($p<0.05$). Other answers like jerking of limbs, changes in behavior did not differ between the groups ($p>0.05$).
Conclusion: Both, medical and non-medical LUHS students had background knowledge about epilepsy. Medical students knew more, especially about specific information. Although, further education about epilepsy is necessary.

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Health science students' viewpoint on epilepsy

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Purpose: Analyse and compare viewpoint on epilepsy between medical and non-medical students of Lithuanian University of Health Sciences.
Method: Students participated in an online survey in which they had to choose correct answers about epilepsy. The survey was sent through the official email system of LUHS in 2022. It was sent to 600 and answered by 228 (38.0%) students - 130 (57.0%) medical and 98 (43.0%) non-medical students (of odontology, nursing, pharmacy, veterinary, etc.). Medical and non-medical student groups did not differ by gender and age ($p>0.05$).
Results: 53 (40.8%) medical and 33 (33.7%) non-medical students have witnessed an epileptic seizure ($p>0.05$). The two groups felt different during the epileptic seizure ($p<0.05$): 13 (10.0%) medical students said that they were feeling as usual compared to 3 (3.1%) non-medical students; medical students felt compassion more often than non-medical students (respectively 21 (16.2%) and 6 (6.1%), ($p<0.05$) . Other feelings like fear or discomfort during the seizure did not differ between the two groups ($p>0.05$).
LUHS medical and non-medical students have similar opinions about the lives of epilepsy patients ($p>0.05$) - they think that people with epilepsy can live a fulfilling life (respectively 83.1% and 77.6%), find a partner (respectively 49,2% and 44,9%), study (respectively 86.2% and 80.1%), choose any profession (respectively 14,6% and 21,2%), be employed (respectively 16,2% and 14,3%), be valued by colleagues (respectively 79,2% and 80,1%), their families' have more issues (respectively 20% and 22,4%) drive a car if epileptic seizures are under control (respectively 68.5% and 71.4%), travel (respectively 83,8% and 74,5%).
Conclusion: The viewpoint on epilepsy did not differ between LUHS medical and non-medical students, although, medical students who saw epileptic seizures more often felt as usual or compassion for the person.

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Examining the financial impact of driving restriction on patients with epilepsy in Ireland

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Purpose: Patients with epilepsy are frequently restricted from driving secondary to seizure. Driving access is often integral to maintaining employment, particularly in rural areas without reliable access to public transportation. We aim to highlight the financial impact of driving restriction in an Irish context, and to recognise important factors affecting patient well-being and livelihood.
Method: Patients were recruited through the Beaumont Hospital neurology service during the period of driving restriction implemented following an epileptic seizure. Patients were subsequently contacted by phone and interviewed using a standardised proforma. Self-reported financial impact of driving restriction included potential loss of employment, change in job, increased costs due to insurance, and combined total loss, estimated in euro/month.
Results: Our analysis includes 23 patients (female 65%, mean age: 45.8 years) interviewed during a period of driving restriction. Our cohort reported a negative financial impact in 61% (n=14) of cases. Another 35% (n=8) reported that their travel options were limited by cost. This was identified as new use of public transport, limited access to public transport and/or use of alternative transport such as taxis. Additionally, 17% of patients (n=4) reported job loss due to lack of driving. Among patients willing to quantify a total value monetary loss per month, 14 patients reported €162.50 (range €20-600) euro per month.
Conclusion: Financial impact is an important and under recognised factor in driving restriction. A majority of patients in our cohort reported a negative financial impact and monetary loss. This has important implications in patient wellbeing and mental health. These findings aim to raise awareness of among clinicians of the indirect, and often not considered, impact of epilepsy and driving restriction.

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Epilepsy care pathway, the Finnish model

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Purpose: Care pathways are used to improve the quality of care by recommending best practices approaches at various stages of a condition. We present the current Finnish Epilepsy

Care Pathway.
Method: On 24 August 2017 Government Decree on the division of labor in specialized healthcare was enacted and Kuopio University Hospital (KUH) became responsible for national coordination of the diagnosis and care of severe epilepsy. A coordinating group was set up composed of representatives from all the Finnish regions in pediatric and adult neurology and the patient organization. Its goal was to enable a seamless diagnostic and care pathway from childhood to adulthood.
Results: **Level 1 or Primary Health Care Level:** identification of the possibility of seizures or epilepsy, and a referral to the level 2 for diagnostics. Patients can be referred back to level 1 for follow-up once seizure-free status is achieved and rehabilitation measures have been planned. If seizures recur or if medication changes are considered, level 2 should be consulted again. **Level 2, or the specialist care:** Diagnosis and treatment of epilepsy and identification of severe epilepsy. The patient is treated at level 2 until seizure-free status is achieved and professional rehabilitation is planned. Patients are offered peer-support by the patient organization at all levels.
Level 3 and 4: When a patient is diagnosed with severe epilepsy, the level 3 unit of a university hospital should be consulted without delay. Level 4 includes: presurgical assessment, intracranial recordings, epilepsy surgery, stimulator implantation (VNS and DBS), and consultations on genetics and epilepsy treatment. Level 4 centers are Epilepsy Helsinki and KUH Epilepsy Center. National multidisciplinary team remote consultations are arranged every second month and if necessary patients are referred to EpiCARE consultation.
Conclusion: The Finnish Epilepsy Care Pathway could serve as a template for other healthcare systems looking for a benchmark.

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Remote counselling services for people with epilepsy: an accessible, cost-effective approach

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Purpose: Rates of depression, anxiety and suicide are much higher in people with epilepsy than in the general population. Scottish Intercollegiate Guideline Network (SIGN) Guideline143 on “The Diagnosis and Management of Adults with Epilepsy” recommends that “treatment of anxiety and depression should be considered as part of a multidisciplinary approach”. There are no statutory services in Scotland available to address the specific mental health needs of people with epilepsy. Access to generic mental health services is limited and subject to ever increasing wait times.
Epilepsy Connections has provided in-person counselling for over a decade. When the pandemic struck, we switched to remote delivery and quickly realised that a remote model would allow us to offer counselling to more people.
Method: Working with partners Quarriers Epilepsy Outreach and Lanarkshire Epilepsy we set up a 12-month pilot project offering remote counselling (Zoom, WhatsApp, video call) to peo-

ple affected by epilepsy.
Counselling was delivered by accredited counsellors and trainees.
The referral pathway was via community-based epilepsy outreach teams. Referrals were assessed using a standardised measure (CORE-10) to screen for depression, anxiety and suicidality, with onward referral where indicated.
Access to broadband, devices, and coaching was provided where needed.
Results: 43 people in 5 health board areas accessed counselling.
Survey feedback indicated a high level of satisfaction:
- 76% of respondents said they felt more in control of their lives
- 65% said they felt less hopeless

- *"I am more confident now"*
- *"I feel a little bit more positive about dealing with my epilepsy"*
- *"It has changed my life completely"*

Conclusion: Remote counselling is attractive to people with epilepsy, cost-effective to deliver, and potentially scaleable.
Counselling services must be properly resourced. Unless attention is paid to the resourcing of administrative and managerial needs it is unlikely that the service will be able to deliver the desired outcomes.

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Parents' expectations about scientific research on Dravet syndrome

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Purpose: A survey was carried out to gather perspectives of parents and caregivers of people with Dravet syndrome (DS) with regards to scientific research. The survey was promoted by Gruppo Famiglie Dravet (Italy), Vereinigung Dravet Syndrome Schweiz (Switzerland) and Dravet Syndrome V. (Germany).
Method: The survey, self-administered through SurveyMonkey, opened in March 2022 and ended on April 10, 2022. It was disseminated through associations' websites and social media and included the following sections: 1) interest in DS research, 2) patient involvement in basic research, 3) data sharing for research purposes and 4) clinical research.
Results: 113 responses were collected. Respondents were located primarily in Italy (43%) and Germany (40%). About 27% of patients were between 1 and 5 years old.
All respondents stated that they are interested in learning about DS research, and refer primarily to the patient organizations for this information. When asked about what research should prioritize, they ranked the following: epilepsy, disease molecular mechanisms, intellectual disability, and SUDEP. Regarding clinical research, 52% of respondents stated that they

would participate in clinical trials, with safety of treatment, risks to worsen, and potential benefits identified as the most relevant information needed before accepting to participate. Respondents agreed that the pace of research depends not only on the availability of adequate funds but also on the extent of collaborations among the various actors in the system. Finally, families are willing to share their data for research purposes, however they feel that it is extremely critical for them to be provided with timely information about the results of the research.
Conclusion: Although preliminary, the results of this survey show how attentive and sensitive the patient community is to the trends in research. The need for information and transparency regarding the research results should drive a revisiting of how we communicate and collaborate with families.

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Interest in and factors influencing people with epilepsy to participate in an exercise intervention trial – results of a brief survey and its preliminary application

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Purpose: To survey people with epilepsy (PWE) about factors that may influence their interest and willingness to participate in a randomized controlled trial (RCT) of exercise intervention and utilize survey results to plan the trial.
Method: A waiver of informed consent was obtained from the University of Alabama at Birmingham Institutional Review Board to survey 100 PWE (18 years and older). Medical records review identified eligible participants. Surveys were administered over the phone or in person (i.e. PWE completed survey during/after their outpatient appointment, or while in the Epilepsy Monitoring Unit). The survey asked about interest and ability to participate in a hypothetical 6-week exercise RCT to investigate whether exercise can improve cognitive function in PWE.
Results: 62 female (ages 40±15) and 38 male (ages 39±15) PWE completed the survey; 69% indicated willingness to participate, with similar proportions of females (68%) and males (71%). The top reason for willingness to participate was they “would like to improve overall health with exercise” (n=49). The top reason for those willing but think participation would be difficult was they “do not have a reliable source of transportation” (n=27). The top reason for not participating was “not interested in research participation” (n=19). Preliminary survey results were used to budget for providing transportation to PWE in planning an RCT, which is now ongoing (NIH R01HD102723; NCT04959019). 27 PWE (63% female; 44% African American/Black, 56% Caucasian/White) have been enrolled to date, and 6/27 (3/6 female; 3/6 African American/Black; 1/6 seizure-free) have used the transportation service offered.

Conclusion: The majority of PWE surveyed were interested in participating in a hypothetical exercise RCT. Accounting for the transportation barrier in the planning of a prospective exercise RCT in PWE has allowed for recruitment of PWE in the current ongoing trial who would otherwise not participate due to lack of reliable transportation.

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Development and evaluation of the usefulness of an electronic diary (e-Diary) for the recording of seizures and other paroxysmal events in alternating hemiplegia of childhood (AHC)

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Purpose: Costumed-designed tools for AHC patients/caregivers in order to record paroxysmal events (epileptic, plegic, dystonic, abnormal eye mouvements, others) with reliability and ease are lacking. We evaluated the usefulness of a smart phone and web accessible version (e-Diary) of an event calendar developed for AHC.
Method: The e-Diary was offered to the participants of 4 European sites (France, Italy, Spain, UK) of the OBSERV-AHC study (IAHCRC consortium). The paper version of the diary was developed by a panel of caregivers and experts in the field.
Mandatory fields for completion included: date, time, duration and type of spells. Caregivers' feedback was evaluated via a telephone survey. IBM SPSS for quantitative data analysis and qualitative analysis for free text comments.
Results: Caregivers' responses of 33 AHC patients [(mean age: 13.5 years (range: 1.8- 41.3 years, SD: 1.8); 51.6% male] were collected. Half of them used the e-Diary with a mean duration of 10.47 months (range 1- 24, SD: 1.96), independently of the frequency of spells. The users mostly appreciated the ease of the reporting (27.6%) and the feeling of contribution to better understanding of the disease (20.7%). The main reasons for no/end of usage were lack of practicality (21.2%) and time (21.2%). 88% of the respondents considered the e-Diary

as a good initiative. 96% (including those that did not use the e-Diary in the context of this study) responded that they could engage to use it in the future (69.7% for more than 2 years) with the condition that some modifications would apply. According to the qualitative analysis, those modifications were mainly with regards to a more user friendly approach.
Conclusion: An electronic version of a disease specific AHC calendar could be useful for families. Modifications according to caregivers' feedback could contribute to its sustainable usage for research and for better patient clinical care.

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The knowledge and awareness of epilepsy among medical students in Poland

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Purpose: Epilepsy is one of the most common neurological disorders. As a chronic disease, associated with long-term treatment with antiepileptic drugs, it can have a negative impact on patients' quality of life. Medical professionals should be well educated and free of prejudices in order to provide adequate care for patients with epilepsy. The aim of the study was to evaluate the knowledge and awareness of epilepsy among medical students in Poland and examine if certain personality traits influence students' view of epilepsy.
Method: The study was conducted on a random sample of 166 Polish medical students from Medical University of Gdansk and Medical University of Warsaw. Participants completed a survey which consisted of their subjective assessment of knowledge of epileptology, actual knowledge of epileptology and their view of stereotypes about epilepsy.
Results: Students from Medical University of Warsaw obtained higher mean score than students from Medical University of Gdansk. Majority of the students have satisfying level of knowledge about epilepsy, however there is still room for improvement, especially in the field of epidemiology, semiology, factors provoking seizures, antiepileptic drugs and most importantly about first aid during seizure. Age and year of study were well correlated with knowledge score and level of awareness of the stereotypes. We found that most personality traits (besides intellect) do not have a strong impact on the level of knowledge about epilepsy, however extraversion and neuroticism have an impact on the awareness of stigma connected to the disease.
Conclusion**:** Polish medical students have sufficient basic knowledge about epilepsy. Academic teachers should put more emphasis on first aid during seizures and awareness of psychosocial challenges associated with the disease. It is crucial for future physicians to not only possess sufficient theoretical knowledge, but also to establish an empathetic doctor-patient relationship in order to provide better care for patients with epilepsy.

Status Epilepticus

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Factors associated with the use of anesthetic drug infusion in patients with status epilepticus and their relation to outcome: a prospective study

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Purpose: The use of continuous IV anesthetic drug infusion (CIVAD) among patients with status epilepticus (SE) has been always questioned for being a risk or a rescue. Studies in limited resource countries in that concern are sparse. This study aims to identify factors associated with the use of CIVAD among Egyptian patients presenting with SE and detect those impact the clinical outcome.
Method: A prospective study involving 144 episodes of SE in 144 patients. Patients were categorized according the use of CIVAD. Subjects underwent clinical assessment, brain imaging, and EEG. The consciousness level was assessed using the Glasgow coma scale (GCS) and the Full outline of responsiveness (FOUR) scale. SE severity score (STESS) and Epidemiology-based mortality score (EMSE) were used as outcome prediction scores. Outcome was judged as end of SE episode within 24 hours, in addition to outcome on discharge (survival versus death).
Results: CIVAD was initiated in 36% of patients (+ CIVAD). Such groups showed a significantly worse initial level of consciousness (< 0.001), an unstable course of seizure evolution (0.009), and all of them showed abnormal EEG patterns. A significantly higher number of patients (+ CIVAD) developed complications (< 0.001) had higher outcome prediction scores (< 0.001), and mortality rates (< 0.001) compared to those who did not need CIVAD (- CIVAD). SE was significantly less likely to end within 24 hours (<.001) among +CIVAD (3, 3.8%) in comparison to -CIVAD (85 ,78.7%). Among +CIVAD, mortality was associated with acute symptomatic etiology (0.02) and higher propofol infusion duration (0.05). Lower initial FOUR scale (p=0.018, OR 3.89) & being intubated at onset (p = 0.002, OR 0.813) were independent predictors for CIVAD use.
Conclusion: CIVAD Initiation depends on multiple clinical parameters among SE patients & might carries higher mortality & thus should be cautiously tailored taking in account its pros & cons.

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External validation of STESS and EMSE as outcome prediction scores in an Egyptian cohort with status epilepticus

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Purpose: There is a lack of data concerning the performance of the outcome prediction scores in patients with status epilepticus (SE) in developing countries. The aim of this study was to compare the predictive performance of the status epilepticus severity score (STESS) and the epidemiology-based mortality score in status epilepticus (EMSE) and adaptation of such scoring system to be compatible with the nature of the society.
Method: This is a prospective study, conducted in Egypt from the period of January 2017 to June 2018.The main outcome measure was survival versus death, on hospital discharge. The cutoff point with the best sensitivity & specificity to predict mortality was determined through a receiver operating characteristic (ROC) curve.
Results: Among the 144 patients with SE with a mean age of 39.3 ± 19.5 years recruited into study, 38 patients (26.3%) died in the hospital with the survival of 99 patients while 7 patients (4.9%) were referred to other centers with an unknown outcome. Although EMSE had a bit larger area under the curve (AUC) (0.846) than STESS-3 (AUC 0.824), STESS-3 had the best performance as in-hospital death prediction score as it has a higher negative predictive value (94.6%) than that of EMSE (90.9%) in order not to miss high-risk patients.
Conclusion: In the Egyptian population, STESS and EMSE are useful tools in predicting mortality outcome of SE. The STESS performed significantly better than EMSEE combinations as a mortality prediction score

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A comparative study of Levetiracetam and Phenobarbital for neonatal seizures as a 1st line treatment

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Purpose: We aimed to evaluate the use of intravenous levetiracetam as the 1st-line treatment of neonatal seizures compared with phenobarbital.
Method: The study was conducted on 104 neonates (0–28 days) with clinical seizures after inclusion criteria. They were assigned in equal ratio into 2 groups; one included neonates who received phenobarbitone (PB), and the other included neonates who received levetiracetam (LEV). Neonates were loaded with 20 mg/kg of intravenous drug-A (phenobarbitone) or drug-B (levetiracetam). In persistent seizures, a second loading dose of the same drug was given. Crossover to other drugs occurred if seizures persisted after the 2nd dose of the same drug. The proportion of neonates who achieved cessation of seizures following the 1st or 2nd loading dose of either drug-A or drug-B (PB or LEV) was the main outcome measure provided that they remained free of seizure for the following 24 hours.
Results: After one or two doses of Levetiracetam or Phenobarbitone, clinical seizures stopped (and remained seizure-free for 24 hours) in 41 (78.84%) and 34 (65.38%) patients, respective-

ly (P 0.01). Neonates in the LEV group showed better seizure control than neonates in the PB group (RR 0.57; 95% CI (0.17, 0.80). We did not report any adverse drug reactions in the LEV group. However, 12 (23.07%) neonates developed adverse drug reactions in the PB Group.
Conclusion: Levetiracetam is considered an effective and safe drug as a first-line AED in neonatal seizures.

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Focal nonconvulsive status epilepticus with impaired consciousness: clinical-EEG data of older adults with and without a previous history of epilepsy

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Purpose: Focal nonconvulsive status epilepticus (focal-NCSE) with impaired consciousness shows variable and nonspecific clinical-EEG data.
Objective: To compare the initial clinical-EEG data of older adults with focal-NCSE, with and without a previous history of epilepsy.
Method: We consecutively evaluated the ictal clinical-EEG aspects and the occurrence of death in 30 older adults with focal-NCSE (10 cases with a history of epilepsy and 20 cases without).
Results: The participants had a mean age of 73.2 years. There were no significant differences regarding age and gender between both groups. In the ictal manifestation, all patients presented alteration in the level of consciousness, without significant differences according to the presence of motor automatisms and vocalization between the groups. The group with a history of epilepsy had a significantly higher occurrence of yawning (Fisher's exact test ; 6[60%] vs 2[10%]; p=007). The etiological factor of focal-NCSE was metabolic/infectious alteration in 6(20%) cases, with structural injury in 17(56.6%) cases and structural injury associated with metabolic alteration in 7(23.3%) cases. There were no differences in the etiological factor and occurrence of previous SE between the groups. The group of individuals without a history of epilepsy had significantly higher TESS scores (≥ 4) (Chi-square test; 17[85%] vs 3[30%]; p=0.004). In 30 days, in 6 (20%) individuals died, but with no difference between the groups. In ictal EEG, 20 cases presented focal electroclinical SE, with lateralized periodic discharges (LPD), rhythmic delta activity (RDA) and/or modifiers-plus in 17 cases. Focal electroclinical SE was significantly associated with the group of individuals with a history of epilepsy and decreased mortality**.**
Conclusion: Focal-NCSE in older adults presents different clinical variables and EEG data according to the presence of a previous history of epilepsy. Mortality was high, without differences between groups. Clinical and EEG data were associated with different etiologies and prognoses. FAPESP2021/09899-2.

Safe and effective implantation and use of vagal nerve stimulation in super-refractory, post-anoxic myoclonic status epilepticus in early pregnancy: a case report

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Purpose: To demonstrate the safety and efficacy of vagal nerve stimulation (VNS) in a pregnant patient presenting with super-refractory post-anoxic myoclonic status epilepticus **(**PAMSE).
Method: This is a retrospective case-study. Information was obtained from the patient's electronic medical records at her local hospital and our centre.
Results: 30-year old female, 5-weeks gestation presented with drug-refractory myoclonic status epilepticus, unresponsive to anaesthetic agents (including propofol, ketamine, and fentanyl), due to drug overdose. The severity of seizures did not allow extubation, and the patient remained ventilated and sedated. VNS was implanted 26 days after seizure onset. The immediate post-operative output was 0.25mA, which was rapidly titrated up to 0.5mA the next morning, and to 0.75mA that afternoon. This was further increased to 1.0mA on 3rd day post-operation, and to 1.25mA 7 days post-op. Myoclonic jerks diminished significantly 5 days post-op, and the patient was extubated. 20 days after VNS implantation, no myoclonic jerks were observed. There was also a notable neurological improvement including increased alertness and mobility, and ability to obey commands. An early pregnancy assessment 17 days after VNS implantation showed normal fetal heart activity, and crown-rump length. Gestational age of 12-weeks + 3-days and a normally-sited pregnancy were confirmed. 19 weeks after VNS implantation there were no further seizures or focal neurology; also no midwifery concerns. The patient delivered a premature but otherwise healthy baby at 33 weeks gestation via a caesarean section.
Conclusion: Super-refractory status epilepticus, specifically super-refractory PAMSE is a challenging diagnosis to manage, which is further complicated by pregnancy due to the teratogenicity of ASMs and ASM polytherapy. This is the first case-study to report the safe implantation and use of VNS during the first trimester of pregnancy for the management of PAMSE. No maternal or foetal complications occurred, and a normal pregnancy was confirmed 17 days after VNS implantation.

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Comparison of pentobarbital and ketamine in super-refractory status epilepticus

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Purpose: It is reported that 11-26% of refractory status epilepticus progress to super-refrac-

tory status epilepticus (SRSE). Pentobarbital infusion has been widely used for treatment of SRSE. More recently, ketamine infusion has been becoming more utilized at a number of institutions. We planned a multicenter retrospective study to compare the efficacy of pentobarbital and ketamine infusion in SRSE. To our knowledge, a comparison of the efficacy of these medications in SRSE has not been performed.
Method: Electroencephalography (EEG) of the patients who were included was reviewed. Each seizure was identified according to American Clinical Neurophysiology (ACNS) 2021 guidelines. When a given epoch appeared to be indeterminate, the epoch was labeled as ictal if the epochs preceding and following that epoch were showing ictal rhythm. Quantitative EEG was judiciously utilized to aid efficient interpretation of recordings. Seizure burden was defined as the duration of seizure in minutes divided by the duration of EEG recording in hours.
Results: Patient 1 was a 49 year-old woman who presented after cardiac arrest. As she continued to be in status epilepticus despite treatment with antiseizure medications (ASMs) and anesthetics, she was started on pentobarbital infusion. Baseline seizure burden was 12.47. Seizure burden during the infusion and after weaning was 0. Patient 2 was a 72 year-old man with history of posttraumatic epilepsy who presented with status epilepticus. Patient was started on ketamine infusion. Baseline seizure burden was 1.37. Seizure burden during the infusion and after weaning was 0.
Conclusion: We present initial portion of our study that compares the efficacy of pentobarbital and ketamine infusion in SRSE. Approximately 70 additional patients will be added to the analysis. They will be assessed for time it took to achieve burst suppression after initiation of infusion, average dose of infusion, mean duration of infusion, and complications, in addition to changes in seizure burden.

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New-onset refractory status epilepticus: a case series of 20 patients focusing on the role of neuronal antibodies in cryptogenic cases

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Purpose: To analyse the etiology and clinical features of new-onset refractory status epilepticus (NORSE) and investigate known or potentially novel autoantibodies in cryptogenic NORSE (cNORSE).
Method: We retrospectively assessed the medical records of patients with status epilepticus at a Swiss tertiary referral center and included adults meeting criteria for NORSE between

2010 and 2021. Demographic, diagnostic, therapeutic and outcome parameters were characterized. We performed post-hoc screening for known or potentially novel autoantibodies including immunohistochemistry (IHC) on rat brain with CSF and serum samples of cNORSE.
Results: We identified 20 patients with NORSE. Etiologies included infections (n=4), Creutzfeld-Jakob disease (n=1), CASPR2 autoimmune encephalitis (n=1), and carotid artery stenosis with recurrent perfusion deficit (n=1). Thirteen cases (65%) were cryptogenic despite detailed evaluation. A posteriori IHC for neuronal autoantibodies yielded negative results in all available serum (n=11) and CSF (n=9) samples of cNORSE. Most surviving patients were seizure-free within one year after discharge (6/8, 75%) with a median modified Rankin Scale of 2.
Conclusion: Neuronal antibodies are unlikely to play a major role in the pathogenesis of cNORSE. Favorable outcomes may be reached in a large proportion of NORSE cases which should encourage clinicians to maintain treatment despite initial refractoriness of status epilepticus.

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Peri-ictal MRI abnormalities in status epilepticus: when do they occur?

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Purpose: Peri-ictal MRI abnormalities (PMA) are seen in status epilepticus (SE). In this study, we aimed investigating how duration of different clinical types of SE determines occurrence of PMA.
Method: Patients with an electro-clinical diagnosis of SE were prospectively recruited between 20/2019 and 12/2022. We included into analysis those patients who underwent an MRI with a specific SE-protocol within the first 48 hours after the onset of SE. We recruited 151 patients (70 women; median age 68 years; IQR 53-76). We divided patients based on semiology type into: 1) Focal motor SE – 59/151, 39%; 2) Convulsive SE (CSE) – 29/151, 19%; 3) Non convulsive (NCSE) with coma– 11/151, 7%; 4) Absence SE – 4/151, 3%; 5) Focal NCSE– 37/151, 25%; 6) CSE-NCSE– 11/151, 7%. We established a cut off value in which the frequency of PMA would be seen in at least 85% of cases.
Results: Median of time between diagnosis and MRI was 13.3 hours (IQR 3-26). PMA were documented in 82 patients (54%). Median of SE clinical duration was 2.7 hours (IQR 1-24). Cut off values for each group were as follows: Focal motor SE (PMA 30/59; 51%) in 6 hours

PMA occurred in 91 %; CSE (PMA 14/29; 48%) in 4 hours - frequency of PMA 100%; NCSE with coma (PMA 6/11; 55%) in 1 hour PMA were seen in 86%; NCSE focal (PMA 24/37; 65%) in 24 hours PMA were seen in 100% and for CSE-NCSE (PMA 8/11, 73%) in 1.6 hours frequency of PMA was 88%. In absence SE no PMA were observed.
Conclusion: Clinical type of SE influences the timing of PMA occurrence. In our cohort, PMA developed earlier in patients with NCSE with coma, CSE-NCSE and CSE as opposed to those with focal NCSE or focal motor SE. In absence-SE PMA were not observed.

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Peri-ictal abnormalities in native and contrast enhanced perfusion: a prospective MRI study on patients with status epilepticus

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Purpose: Perfusion MRI abnormalities such as ictal hyperperfusion or post-ictal hypoperfusion are common in patients with status epilepticus (SE). We aimed investigating concordance between cerebral blood flow (CBF) of contrast enhanced MRI perfusion and arterial spin labeling (ASL; native perfusion) in patients with SE.
Method: We prospectively recruited 132 patients (median age 70 years (IQR 55-77), 66 women) with SE who underwent MRI within the first 48 hours after SE onset between 02/2019 and 12/2022. Standard MRI protocol included ASL and contrast enhanced perfusion among other sequences. We excluded nine patients from the analysis: four with a hyperperfusion related to a brain tumor, four with bilateral hyperperfusion, and one patient with luxury hyperperfusion due to subacute stroke. In total 123 patients were further analyzed. Visual qualitative analysis was followed by a quantification of the region showing perfusion abnormalities. In the quantification analysis, we compared the lesion side to the contralateral healthy side in both, ASL and contrast enhanced MRI perfusion. Quotients of difference were calculated.
Results: Perfusion abnormalities were seen overall in 54/123 (44%) of patients. Hyperperfusion was observed in 46/54 (85%) of patients, while 8/54 (15%) of patients had hypoperfusion.
The means of difference quotients were as follows: in ASL for hyperperfusion 2.1 (SD 0.7) and for hypoperfusion 0.7 (SD 0.4); in contrast-enhanced perfusion for hyperperfusion 1.5 (SD

0.3) and for hypoperfusion 0.8 (SD 0.1). There was a strong overall correlation between ASL and CBF quantification (Pearson coefficient: 0.8).
Conclusion: Both**,** ASL and contrast-enhanced perfusion MRI performed well in identifying SE-related perfusion abnormalities. We found a strong correlation in the quantification of affected regions compared to the contralateral side for both sequences. Therefore, ASL could be considered as a reliable alternative of contrast
enhanced MRI perfusion in patients with SE.

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Semiology of status epilepticus and its risk of peri-ictal abnormalities: aq prospective MRI study

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Purpose: Peri-ictal MRI abnormalities (PMA) may occur in patients with status epilepticus (SE). However, it remains unclear who will develop these abnormalities. In this study, we aimed to determine if semiology type of SE might predict occurrence of PMA.
Method: Patients with an electro-clinical diagnosis of SE were prospectively recruited between 02/2019 and 12/2022. We included into this analysis those patients who underwent an MRI with a specific SE-protocol within the first 48 hours after the onset of SE. Patients with an EEG pattern corresponding to an ictal-interictal continuum, patients with prominent movement artifacts and patients with a hypoxic brain injury due to cardiac arrest were excluded from the analysis. Incidence of PMA was estimated for each semiology group of patients.
Results: We prospectively recruited 151 patients (70 women; median age 68 years; IQR 53-76). Median of time lapse between diagnosis and MRI was 13.3 hours (IQR 3-26). SE with prominent motor symptoms was observed in 88/151 (58%) patients; non-convulsive SE (NCSE) – in 52/151 (34%) and convulsive SE (CSE) which developed into NCSE (CSE-NCSE) – 11/151 (7%). PMA were documented in 82/151 (54%) of patients. PMA were documented in 44/88 (50%) of patients with prominent motor symptoms SE; in 30/52 (58%) patients with NCSE and in 8/11 (72%) of patients with CSE-NCSE. In the group of patients with NCSE, patients with focal-NCSE were most frequently associated with PMA - 24/37(65%). In patients with NCSE in coma, PMA were documented in 6/11 (55%). However, none of patients with

the absence-SE showed PMA. The above-mentioned differences, however, were not statistically significant.
Conclusion: In our cohort of patients, patients with CSE-NCSE were most frequently associated with PMA, followed by those with focal NCSE. In patients with absence SE, PMA were not observed.

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Hypocretin-1/Orexin-A and excessive daytime sleepiness in patients with nonconvulsive status epilepticus

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Purpose: Nonconvulsive status epilepticus (NCSE) manifests clinically by a change in the mental state without coma or coma following a generalized tonic-clonic seizure. The neuropeptide hypocretin/orexin (H/O) maintains wakefulness and sleep. Epworth Sleepiness Scale (ESS) is a subjective scale of Excessive daytime sleepiness (EDS) assessments. Polysomnography (PSG) and multiple latency sleep test (MSLT) are objective methods of assessing sleep and daytime sleepiness.
Method: We present a pilot proof-of-concept prospective non-randomized monocentric clinical trial. We enrolled consecutive patients meeting inclusion/exclusion (IC/EC) criteria. We collected cerebrospinal fluid, MRI brain scan, PSG, MSLT, and assessment of EDS (ESS; cut-off value ≥ 10 points). The normal range of H/O is 200-700 pg/ml. A cut-off value of apnea/hypopnea index (AHI) in sleep-disordered breathing (SDB) was ≥ 5. We presented categorical data as numbers (percentage) and continuous and ordinal data as median and IQR.
Acknowledgments: The project funded University Hospital Ostrava; grant 09/RVO-FNOs/2020.
Results: From May 2020 to November 2022, we enrolled 12 patients; seven (58.3 %) women were aged 70 (17.5) years. Eight patients (66.7%) had ischemic lesions at brain MRI scans. The H/O level was 244 (61) pg/ml, and three (25%) patients reached levels below 200 pg/ml. The ESS was 5.5 (3) points. PSG study: Total sleep time was 322.2 (247.8) minutes. Rapid eye movement (REM) sleep decreased to 2.9 (5.6) %. Sleep latency (SL) at PSG was 6 (22), and at MSLT, 6.8 (9.7) minutes. We objectively proved EDS in eight (66.7%) cases. We diagnosed SDB in 8 (66.7%) patients, mainly obstructive sleep apnea (OSA) based on parameter AHI of 5.65 (26.3) and an oxygen desaturation index (ODI) of 1.0 (10.0).

Conclusion: Patients with NCSE have excessive daytime sleepiness, shorter sleep latency, and reduced REM sleep. Hypocretin-1/orexin-A levels decreased in 25 % of cases. There is a high occurrence of obstructive sleep apnea in patients with NCSE.

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Status epilepticus secondary to T-cell encephalitis, take action before it gets too late

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Purpose: Half of patients with New-Onset Refractory Status Epilepticus (NORSE) have autoimmune etiology. Treatment of autoimmune NORSE includes combination of anti-seizure medicine (ASM), and immunotherapy. Definite diagnosis of T Cell encephalitis requires brain biopsy. However, there are no guidelines on when a biopsy should be performed. In this abstract we discuss two cases of super-refractory NORSE of T Cell etiology.
Method:

- Case1: Twenty-year-old female, with multiple focal clinical seizures, and Continuous EEG (cEEG) revealing status epilepticus (SE). Seizures were not controlled with Midazolam, Levetiracetam, Lacosamide, Diazepam, Perampanel, Valproic acid, Ketamine, Pentobarbital, hypothermia protocol, 8 days of IVMP, 5 days of IVIG, 5 sessions of plasma exchange. She underwent right frontal lobe biopsy on day 39 of symptoms that revealed T cell infiltration. Cyclophosphamide was administered on day 47 and seizures were completely controlled within two weeks.

- Case 2: 28-year-old male, presented with generalized tonic clonic seizures and cEEG consistent with SE. Midazolam, Levetiracetam, Lacosamide, Pentobarbital, Clobazam, Phenytoin, Perampanel, Topiramate, Phenobarbital, magnesium, Gabapentin, Hypothermia, 5 days of IVMP, 5 sessions of plasma exchange, and Rituximab did control his seizures. Right frontal lobe pathology on day 12 of symptoms, was indicative of T Cell Encephalitis. Seizure freedom achieved two weeks after cyclophosphamide infusion on day 19 of symptoms.

Results: In both cases, seizure control was achieved only after appropriate immunotherapy to attenuate cellular immunity Case 1 who received cyclophosphamide on day 47 had worse outcomes, currently on six ASMs and RNS, having one seizure per week. In addition, she has severe anterograde memory loss. While case 2, who was treated earlier, has rare seizures on 3 ASM.
Conclusion: Seizure control was achieved when T cell nature of encephalitis was revealed through biopsy. Therefore, we propose considering early brain biopsies when autoantibody negative patients with super-refractory seizures do not show any response to 2 first line im-

munotherapies.

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A multimodal approach to predict short term outcome after status epilepticus: the ADiReN score

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Purpose: Short-term prognosis after SE has been explored mainly in terms of mortality and disability development. Three different prognostic scores have been proposed to assess short term mortality: STESS (Status Epilepticus Severity Score), mSTESS (modified STESS) and EMSE (Epidemiology-based Mortality score in Status Epilepticus).
We evaluated the role of serum levels of Neurofilament light chains (NfL) and S100B to predict 30-days mortality and refractoriness to treatment. We developed a new score based on a multimodal (clinical-electroencephalographic-biochemical) approach to predict short-term mortality and compared its predictive accuracy to the existing prognostic scores.
Method: Serum levels of NfL and S100B in adult patients with SE were evaluated. All samples were acquired within 72 hours from the diagnosis. The predictive power of these biomarkers toward short-term mortality and refractoriness to treatment was assessed.
Results: Serum NfL and S100B were measured in 87 patients (female 62%; median age 70 years). Serum levels of NfL were significantly higher in refractory compared to responsive SE episodes, while no differences were found for S100B. NfL (cut-off 19.75 pg/ml) was an independent predictor of refractoriness development (OR 8.2 95% CI 2.08-32.58 p = 0.003) and of 30-days mortality. Values of NfL ≥70.25 pg/ml were associated to a significantly lower cumulative survival (log rank test: 0.002) after the adjustment for age (HR 5.26, 95% CI 1.16-23.78, p = 0.031). Finally, we proposed a new multimodal prognostic score for short-term mortality, so called ADiReN score (**A**ge **Di**sability **Re**fractoriness **N**eurofilament), that showed a higher discriminative power (AUC of 87.5%; 95% CI 79%-95.9%) and positive predictive value for death compared to existing clinical scores.
Conclusion: Serum NfL measurement within 72 hours from SE diagnosis could help predicting treatment refractoriness and short-term mortality. We propose a new prognostic score based on a multimodal evaluation that outperforms already established scores.

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Systematic review about the Diisopropylfluorophosphate mouse, rat and in vitro models with cholinergic induced-seizure

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Purpose: We aim to summarize the data found in peer-reviewed papers about the effects of Diisopropylfluorophosphate(DFP) on the Central Nervous System in mouse, rat and *in vitro* models.
Method: This review was carried out using the National Library of Medicine. We used keywords such as "diisopropylfluorophosphate", "epilepsy", "status epilepticus", "seizure" and "CNS" and separated bibliographic information in 3 groups based on the three experimental models. Altogether, there are 64 papers of which 54 use rats, 6 use mice and 4 use *in vitro*.
Results: DFP causes the onset of electrocorticographic seizures and induces neurodegeneration at 24h post exposure(PE), 7 days PE(DPE) and 28 DPE on adult mice. Moreover, mice present an increase of microglia and astrocyte's area in cortex and hippocampus and an increase in cytokines of microglia/macrophages and astrocytes at 1h, 4h, 24h, 3 DPE, 7 DPE and 28 DPE.
Adult rats present an increase in neurodegeneration, neuronal activity, neuroinflammation from 60min to 24h PE and also at 2, 3, 4, 7, 8, 14, 21, 28, and 42 DPE, as well as 1-2 months, 3 months and 6 months PE. DFP also increases oxidative stress and induces calcium accumulation on necrotic cells and a leakage of the blood-brain barrier. Pretreatments used on rat and mouse model attenuate the seizures.
DFP induces spontaneous frequent bursting in CA3 on hippocampal slices. Atropine pretreatment delays the onset of the bursting and physostigmine pretreatment prevents slices from burst.
Conclusion: In conclusion, the animal model mostly used is the rat. However, each paper analyses the DFP effect at different time points. Therefore, it is difficult to synthetize all the information. Moreover, it would be necessary to study DFP exposure on rats at early stages. Finally, it would be necessary to find a treatment that could be used after DFP intoxication instead of a pretreatment.

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Super-refractory status epilepticus with a genetic cause: a case study

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Purpose: Super-refractory status epilepticus (SRSE) is continuous or recurrent seizure activity that does not respond to first- or second-line treatments, or recurrence of SE within 24hrs following therapeutic coma. We describe the case of a previously well controlled patient with epilepsy who presented with SRSE of genetic aetiology.

Method: 47-year-old lady with a mild intellectual disability (ID) and epilepsy who had been seizure free on valproate and Levetiracetam for 7 years presented following an unprovoked witnessed convulsion requiring buccal midazolam. On arrival to the emergency department she had several seizures requiring intubation and transfer to the intensive care unit.
Bedside electroencephalogram on Propofol and Midazolam infusions demonstrated non-specific generalised slowing, but no ongoing seizures. Repeat 3 days later whilst still on sedation revealed generalised bursts of polyspike activity with a bi-anterior predominance, confirming SRSE.
Results: Repeated MRI, lumbar puncture and paraneoplastic screens were negative. Given her history of mild ID a blood sample was sent for genetic testing. A mutation of the ALDH5A1 gene for production of succinic semialdehyde dehydrogenase (SSADH) was identified. SSADH is involved in the breakdown of gamma aminobutyric acid, the main inhibitory neurotransmitter.
Numerous sedating agents, anti-seizure medications, steroids, intravenous immunoglobulin and a course of electroconvulsive therapy were tried.
Conclusion: SSADH deficiency (SSADHD) is a rare metabolic disorder caused by mutations of the ALDH5A1 gene. Its phenotypic spectrum is broad and varies in severity (ID, ataxia and seizures) . It has linked with cases of sudden unexplained death in epilepsy in previously well controlled patients. Vigabatrin works by decreasing the production of SSADH, making it a potential targeted treatment option for SSADHD. Our patient did not respond clinically or electrographically. This case highlights the need to consider genetic testing even in cases of well controlled epilepsy as our knowledge of precision therapeutics within the field expands.

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Genetic variants associated with atypical absence status epilepticus

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Purpose: Atypical Absence Status Epilepticus (AASE) is a generalized non convulsive Status Epilepticus (Trinka et al. Epilepsia 2015;56(10):1515) occurring in patients with epileptic encephalopathies such as Lennox-Gastaut, Angelman, Dravet syndrome and others (Fernández-Torre et al. Expert Rev Neurother 2015;15:1455–73). To our knowledge, no comprehensive review of the genetic basis of this condition has been performed. The aim of this study is to present the electroclinical findings of a patient with this predominant clinical manifestation and a genetic aetiology and to review the literature on this topic.
Method: The patient underwent an extensive EEG, laboratory and neuroradiological study as well as genetic testing. The results of the functional MRI studies performed in this patient have been previously published (Cioclu et al. Front Neurol. 2021 Sep 9;12:722664). A

literature search on Pubmed was made using different combinations of the terms “atypical absence status epilepticus”, “non convulsive status epilepticus”, “status epilepticus”, “atypical absence”, “DEE”, “developmental and epileptic encephalopathy”, “genetic”, “epilepsy”. Only articles in English were reviewed. We excluded the cases with a significant myoclonic component involving the limbs.
Results: The patient presented recurrent episodes of atypical absence status epilepticus, often with associated eyelid myoclonia. Genetic studies uncovered a de novo likely pathogenic variant in *NEXMIF*. The genetic conditions more often associated with AASE in literature were pathogenic variants in *UBE3A, SCN1A, NEXMIF*, ring chromosome 20, 15q11-13 deletions, 4p deletion; others, more rarely reported were variants in *SYNGAP1, CUX2, CNKSR2, KCNH2, SCN8A*.
Conclusion: No gene or copy number variant emerged as uniquely associated with AASE and it is worth noting that not all conditions associated with atypical absences are equally associated with the occurrence of AASE. We present the electroclinical picture of a patient with *NEXMIF*-associated developmental and epileptic encephalopathy and recurrent episodes of status epilepticus.

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Status epilepticus in Brunei Darussalam: etiology, semiology and its electrographic characterization

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Purpose: Status epilepticus is a neurological emergency that has significant mortality and morbidity and is divided into convulsive and non-convulsive status epilepticus. The Brunei Neuroscience, Stroke and Rehabilitation Centre (BNSRC) serves as the tertiary Neurosciences in Brunei providing neurology services. Our main objective was to determine the etiology of status epilepticus in Brunei, its semiology and its electrographic characterization.
Method: Between January 2020 and December 2020, data were collected retrospectively from BRUHIMS for patients over the age of 12 admitted to an Intensive Care Unit treated for status epilepticus.
Results: Eleven (11) patients were identified to have status epilepticus with majority were females (63%). The mean age of the patient was 48. The identified etiology of status epilepticus were three cases secondary to CNS infection (28%), two patients were diagnosed with autoimmune encephalitis (18%), two had history of cerebrovascular accidents (18%), two presented with breakthrough seizures (18%), one had toxic metabolic abnormalities (9%) and one had history of meningioma (9%). Seven presented with convulsive status epilepticus (64%), and four had non-convulsive status epilepticus (36%). The main EEG characterizations were mostly continuous electrographic status epilepticus (54%), multifocal discharges (18%), and one had focal epileptiform activity with secondary generalization. However, two had nor-

mal EEG (18%) in which case one had history of pseudoseizure, and the other case had been treated for presumed meningoencephalitis and EEG was delayed.
Conclusion: This was the first case series on Status epilepticus in Brunei Darussalam. Our findings showed that the most common presentation was convulsive status epilepticus and infection being the most frequent etiology identified as comparable with other audits globally.

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Autoimmune-associated epilepsy as the outcome of autoimmune encephalitis with NORSE presentation

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Purpose: New-onset refractory status epilepticus (NORSE) can be the clinical presentation of autoimmune encephalitis (AE) in about half of the cases [1]. This study evaluates risk factors for developing chronic epilepsy as the outcome of a definite or probable AE [2] with NORSE presentation.
Method: In this retrospective observational multicenter cohort study, patients with definite or probable AE with NORSE as the presenting symptom were enrolled.
Results: Sixty-four patients (22 children, 42 adults) were enrolled and followed up for a median time of 31 months (range: 12-192). Five patients died during the SE. Epilepsy was present in 49.15% at the final follow-up, with a prevalence in probable antibody-negative AE (p=0.002) and in patients with older age at SE onset (p=0.02). Early immunomodulatory treatment (p=0.004) and the administration of second-line agents (p=0.009) were associated with a more favorable outcome with seizure freedom at the end of follow-up, while a poor response to immunotherapy during the acute phase (p=0.003), a longer duration of SE (p=0.01), and NORSE with prominent motor symptoms (p=0.04) were related with the development of autoimmune-associated epilepsy.
In the multivariate analysis, independent predictors of developing epilepsy were probable antibody-negative AE (p=0.04) and SE with prominent motor symptoms (p=0.04).
Conclusion: Epilepsy is a frequent sequela of defined or probable AE, occurring in 43.73% of cases [3]. Clinical presentation with NORSE is an unfavorable prognostic factor, with the risk of developing epilepsy in approximately half of the cases. Early identification of the etiology of the status epilepticus and the prompt institution of tailored treatment are associated with a more favorable outcome.

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Treatment of established new-onset status epilepticus (E-NOSE): a real-word multicenter experience

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Purpose: New-onset status epilepticus (NOSE) is a condition characterized by prolonged seizure lasting >5 minutes or the presence of recurrent seizures without recovery to baseline in between in patients without a defined epilepsy history. Up to 50% of patients with NOSE are refractory to benzodiazepine treatment, a condition known as established status epilepticus (SE). In this context, anti-seizure medication (ASM) therapy is generally recommended, even if no major recommendation about the most effective one is available. This study aims to com-

pare the efficacy of the most common ASM employed for the treatment of established NOSE (E-NOSE).
Method: In this retrospective, multicenter, observational study adult patients with diagnosis of E-NOSE were retrospectively selected between January 2016 and December 2022 in three third-level hospitals in the center of Italy. Demographics and clinical data as well as diagnostic work-up and treatment were reviewed in all included patients. We considered as effective the ASM that was the last drug introduced or increased in dose before termination of E-NOSE and without changes in the comedication.
Results: 123 patients were included in the study. The mean age of the final study cohort was 67.9 ± 17.3, with 49 men (40%). After an extensive diagnostic workup, E-NOSE etiology was defined in 109 cases (89%). In the total cohort, phenytoin (PHT) showed the highest response rate (62.1%), followed by valproate (VPA) (42.9%) and lacosamide (LCM) (30%). The comparison among all the employed drugs showed PHT as the most effective ASM (p=0.005). In the pairwise comparisons, VPA was superior to levetiracetam (LEV) (p=0.02), but not to LCM (p=0.65). PHT had a significantly higher resolution rate compared to LEV (p=0.0005) but not to LCM (p=0.16). Thirty-one patients (25%) developed a refractory status epilepticus.
Conclusion: PHT showed the higher effectiveness in E-NOSE management. Furthermore, LCM and VPA can represent good therapeutic options.

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The combination of ketamine-dexmedothymidine reduces status epilepticus in dogs. the dog as a natural model in status epilepticus

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Purpose: The objective was to evaluate the efficacy of the ketamine-dexmedothymidine (KD) combination on refractory status epilepticus (RES) in dogs.
Method: Dogs (n=12) with seizures between 24-120 hours (mean 27h) that did not respond to one or two first-choice anticonvulsant drugs in the correct dose and to one anesthetic drug (propofol) were included. The response of the combination of both drugs was evaluated at a dose of 1 mg/kg/h and 5 µg/kg/h iv for an average of 13 hours until the termination of refractory status epilepticus.
Results: 75% of the dogs (n=9) yielded to subsequent seizures with continuous infusion of KET-DEX with a duration between 9-18 hours of infusion (mean=13.5h) 25% (n=3) continued with seizures convulsive
Conclusion: With these results, we could conclude that the blockade of glutamatergic neurotransmission and the increase in adrenergic neurotransmission in combination reduce the EER in dogs, decreasing calcium entry and glucose metabolism in structures related to seizures in these animals.

Terminology and Classification

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The seizure termination project: expert consensus recommendations for the rapid termination of seizure emergencies

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Purpose: Seizure emergencies experienced by patients with epilepsy include seizure clusters (SC), prolonged seizures (PS) and status epilepticus (SE). The concept of rapid epileptic seizure termination (REST) has been suggested as a potential treatment goal for certain seizure emergencies (Asnis-Alibozek A, et al. Epilepsy Behav Rep 2021;15:100409). While there is international guidance around definitions and management of SE, in the absence of evidence-based guidelines for PS and SC, this project aims to develop expert recommendations for rapid termination of seizure episodes to prevent progression to a higher-level emergency.
Method: In this first phase of the Seizure Termination Project, 12 members of the expert working group, comprising epileptologists, neurologists and pharmacologists from Europe and North America, utilized a modified Delphi consensus methodology to vote anonymously on statements regarding classification and management of seizure emergencies. Consensus was defined as ≥75% voting 'Agree'/'Strongly agree'. In the next phase, expert recommendations that reached consensus will be put forward to a larger panel of approximately 20 expert advisors.
Results: The expert working group agreed REST is a viable concept and the following statement reached consensus with 100% of advisors voting 'Strongly agree': "An ideal REST (or acute seizure termination) treatment would start to act within 2 minutes of administration to terminate ongoing seizure activity." The expert working group reached consensus on terminology defining different types of PS and SC. Consensus was also reached on goals and potential benefits of rapid seizure termination and specific patient/seizure types that could benefit most from rapid termination. Recommendations on timing of treatment administration for different seizure types also reached consensus.
Conclusion: The expert working group had a high level of agreement on recommendations for defining and managing seizure emergencies amendable to rapid termination. Further

work is ongoing to validate these recommendations to support optimal seizure emergency management.

Funding: UCB Pharma-sponsored.

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In patients with temporal lobe epilepsy: is it syncope or drop attack?

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Purpose: We describe a patient with refractory temporal lobe epilepsy, had a fall resulted in significant head injury and the use of the term syncope vs drop attacks describing the fall.
Method: 52 years old right-handed male with refractory temporal lobe epilepsy for 22 years, on triple AEDs and had a prior trail of 4 AEDs which were not efficacious. He usually describes his seizures as feeling dizzy, loose awareness and falls, and subsequently amnestic to the events. These focal onset seizures rarely evolve into GTC. A year prior during focal seizures with impaired awareness he had two falls 4 months apart resulted in bifrontal and left temporal contusion and skull base fracture. He is admitted into EMU for prolonged Video EEG and subsequently had brain imaging and neuropsychology evaluation part of phase 1 presurgical assessment.
Results: The Video-EEG confirm right temporal lobe focus. However, during the seizures of focal with impaired awareness, he had bradycardia and asystole on ECG. The patient was assessed by cardiology and a permanent cardiac pacemaker was placed. This supported the falls that occurred last year which resulted in significant traumatic brain injury. The cortical representation of sympathetic nervous system on the right and parasympathetic on the left. However, our patient had the focus on the right temporal lobe which support some representation of parasympathetic on the right as well, as has been reported in the literature.
Conclusion: Obviously drop attacks can occur in Temporal Lobe Epilepsy, however, the term syncope should be avoided as the literature dissuade clinicians from using EEG in the diagnosis of syncope. Equally, this finding also supports the notion that some parasympathetic in addition to the sympathetic nervous system are represented on the right hemisphere.

Late Breaking Abstracts

Adult Epileptology

1444

Brain conductivity estimated from SEEG low-intensity stimulations correlates with epileptogenicity

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Purpose: Using a new method for measuring brain electrical conductivity from SEEG stimulation (Carvallo et al. IEEE 2018), we evaluated the hypothesis that brain conductivity is correlated with the degree of epileptogenicity, in 16 patients with drug-resistant focal epilepsies.
Method: We used bipolar stimulations at 5 Hz and 0.2 mA (biphasic, charge-balanced pulses of 500 µs per phase) followed by a method estimating conductivity based on biophysical modelling of brain response to pulse stimulation. We evaluated the degree of epileptogenicity using a semi-automatic quantitative method: the epileptogenicity index.
Results: We performed 1034 stimulations of 511 structures. We found that brain conductivity is lower in the epileptogenic zone (mean difference = 0.0934, p = 0.0002) and correlated with the value of epileptogenic index (p<0.001, Rho = -0.26). This anti-correlation was observed in 13/16 patients. Conductivity was higher in some specific lesions (tuber, polymicrogyria, and NDT) and lower in FCD and in the insula. A multivariate analysis showed that conductivity remains significantly associated with the level of epileptogenicity independently from the inter-patient variability, the presence of lesion and the lobe stimulated. Looking at the predictive value of conductivity for epileptogenicity, overall AUC was equal to 0,626 (best cut-off value = 0.43, sensitivity= 79, specificity= 44, PPV= 87, NPV= 31, Youden's index = 0.231).
Conclusion: Using a new model-based method for estimating brain conductivity from SEEG pulse low intensity stimulations (easily implemented in clinical routine), we found lower conductivity in epileptogenic than in non-epileptogenic zones. Thus, conductivity may be a new and complementary biomarker of epileptogenicity that can be used in SEEG. Possible pathophysiological bases may be changes in extracellular space volume (+/- tortuosity) in epileptic tissue.

1470

Clinical and electrophysiological characteristics of patients with bilateral, simultaneous upper extremity automatism

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Purpose: This study aimed to evaluate semiological findings regarding lateralization in patients with bilateral upper extremity automatism and its effect on seizure freedom after surgery.
Method: Seven hundred ten patients followed up in our Neurology Clinic, Istanbul University, Istanbul Medical Faculty, whose seizures were recorded in the video electroencephalography monitoring (VEM) unit between May 2009 and November 2021 were evaluated retrospectively. Thirty-one patients (15 male, 16 female) were found to have simultaneous, bilateral automatism in their upper extremities during their seizures. Demographic characteristics, ictal and interictal EEG findings of 140 seizures of these patients, and prognostic features in patients who underwent surgery were analyzed.
Results: The mean age was 39.1±13.3; the epilepsy onset age was 14.1±8.2; the follow-up was 8.9±7.7 years. Twenty-six patients had temporal lobe epilepsy (TLE), three had frontal, 1 had occipital, and another had temporooccipital lobe epilepsy. Except for bilateral upper extremity automatism, no lateralizing or localizing semiological finding was detected in all seizures of nine patients. Three of these nine patients were operated on and were seizure-free in their 1st-year post-op. All of these patients had hippocampal sclerosis (HS) on MRI, and their ictal and interictal findings were consistent with the HS side. Of the six patients who were not operated on, three had extratemporal lobe epilepsy of unknown cause; the epilepsy etiology of the remaining three TLE patients was HS in one, cavernoma in the other, and one TLE of undetermined cause.
Conclusion: Bilateral upper extremity automatism can be observed in the presence of TLE and HS. Without any other semiological finding, a good prognosis can be seen after surgery in cases where cranial MRI and interictal/ictal EEG findings are compatible.

1474

Do not rule out idiopathic generalized epilepsy because déjà vu: a systematic review

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Purpose: 'Déjà vu' (DV) is a French term that describes an inappropriate impression of familiarity of present experience with an undefined past. It has been classically associated with focal seizures arising from medial temporal lobe. However DV is occasionally described in idiopathic generalized epilepsies (IGE). We aimed to evaluate the presence and frequency of DV in IGE.
Method: We used the Preferred Reporting Items for Systematic Review and Meta-Analysis for protocols (PRISMA-P) and searched PubMed and Embase from January 2000 to July 2022.
Results: 5 studies were included with a total of 1177 IGE and 1146 with focal epilepsy (FE) patients. The frequency of DV in IGE ranged from 0 to 11%, and the average was 3%, compared to 19.1% in FE. Broadly, any type of aura was reported by 40% in IGE. EEG correlate of DV in IGE was not appropriately evaluated in the studies.
Conclusion: DV phenomena is described in PWE with IGE and should not be taken for granted as equal to temporal lobe epilepsy symptom. Recognition that DV and other forms of auras are relatively common in patients with IGE is important to clinicians and may prevent misdiagnosis of FE and incorrect investigation and therapeutic choices.

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EpiCare@Home: remote wearable seizure monitoring for people with epilepsy can improve

delivery of care

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Purpose: For people with epilepsy, the journey to adequate treatment and an acceptable quality of life may be long and cumbersome. Hence, we developed EpiCare@Home based on extensive clinical research (NCT04284072, NCT04642105, NCT04584385) as a remote monitoring service to support neurologists and generate long-term insights into seizure frequency and burden outside the hospital.
Method: After a telemonitoring prescription by a neurologist, patients were set up with unobtrusive wearable technology (Sensor Dot) during a consultation or directly at home for 1-3 days up to 2 weeks. Sensor Dot measures 2-channel behind-the-ear EEG, ECG (heart rate, respiration rate), and motion (accelerometer, gyroscope and activity index). Patients or caregivers used the Assistant App as a digital seizure diary and the healthcare provider used the dashboard to manage patients and visualize recorded raw data with annotated potential epileptic events.
Results: A total of 36 subjects diagnosed with (or suspicion of) generalized (33) or focal-onset epilepsy (3), were included. A retrospective case review was done to assess the clinical value. We captured 626 potential epileptic events, including typical and atypical absences, Generalized-tonic-clonic (GTCs), and Focal impaired awareness (FIAs) where the epileptic activity was linked to a diary event (clinical seizure), whereas in other cases these events were unclear or missed by the patient. In 84% of cases (30), a positive, direct clinical impact, defined as the ability of the real-world data to support a clinical decision, was achieved after a multi-day follow-up outside the hospital. In the remaining 16% of cases, no clinical decisions were derived due to low EEG quality (2) or uncertainty (4) around the epilepsy diagnosis.
Conclusion: We demonstrate the potential importance and clinical utility of remote patient monitoring in epilepsy care. In 84% of cases, a direct positive clinical impact was achieved by supporting timely diagnostic decision-making that can improve the standard of epilepsy care.

1511
The use of illicit psychoactive substances in people with epilepsy

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Purpose: The aim of this study was to assess the prevalence of active and previous use of illicit psychoactive substances (IPS) in people with epilepsy (PWE). Secondary objectives were evaluation of effect on seizure control and the knowledge of PWE about possible effects of IPS on epilepsy.
Method: The study was conducted from January 2021 to December 2022 in Vilnius university hospital and included consenting patients with epilepsy aged 18 to 65 who filled an anonymous questionnaire about their epilepsy, seizures, medications and experience with IPS. Active use of IPS was defined as

occuring during the past twelve months. Study was approved by Vilnius regional bioethics committee (approval No 2019/12-1173-661).
Results: The study included 258 consecutive subjects with the mean age of 32.87 ± 11.79. Females accounted for 51.16 % participants. Duration of epilepsy was 14.41 ± 12.9 years. Seventy-four (28.68 %) participants reported previous and 34 (13.18 %) current use of IPS. Most popular IPS were cannabis (61 (23.64 %)), sedatives other than prescribed for epilepsy treatment (23 (8.91 %)), cocaine (11 (4.26 %)) and ecstasy (10 (3.87 %)). The use of IPS were not associated to epilepsy characteristics (all; p <0.05). Only 49 (18.99%) subjects reported to have received enough information from their physicians while 48 (18.6%) searched for information themselves. The decrease of seizure frequency was reported by 12 (19.67 %) and seizure severity – by 7 (11.48 %) users of cannabis. The deterioration of seizure control was reported by three participants (using cannabis, ecstasy and sedatives).
Conclusion: The use of IPS in PWE is comparable to general population. Only a minority of patients have sufficient information about IPS effect on seizures and epilepsy. The majority of PWE do not notice IPS-related improvement or deterioration of epilepsy.

1517

Validation of SERIAS, a novel self-report instrument to measure the impact of epilepsy

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Purpose: To create and validate the Seizure-Related Impact Assessment Scale (SERIAS). This novel patient reported outcome measure (PROM) compares the 'trade-off' between seizures and treatment-related side effects, and measures epilepsy-related disability qualitatively and quantitively. It fills an important gap in PROMs for epilepsy clinical trials and practice. A similar migraine-specific PROM is the most implemented condition-specific PROM used in new neurological drug approvals in Europe.
Method: Adults with epileptologist-confirmed epilepsy from two Australian Epilepsy Centres are being recruited. People with functional seizures or unable to self-complete English-language validated instruments are excluded. Participants providing informed consent are invited to complete questionnaires at baseline, 3- and 6-months later. SERIAS includes 5 questions that ask number of days per month that seizures or treatment-related side effects partially or fully impact work/home/school and family/social/non-work activities, as well as a visual analogue scale (VAS) regarding epilepsy-related disability. SERIAS is completed alongside 7 internationally validated instruments measuring treatment side effects, mood disorders, and quality of life. Data are securely managed in the Research Electronic Data Capture (REDCap) online platform. Target recruitment is n=100, ensuring >50 people complete all questionnaires at all timepoints. Bivariate correlation coefficients between the SERIAS and other relevant instruments will be computed. Psychometric reliability will be computed in the form of Cronbach's alpha and McDonald's omega coefficients.
Results: Recruitment commenced March 2023. To date, 50 people (F n=32, median age 41years [IQR:34-52]), have completed baseline questionnaires. Epilepsy type is focal (n=34), generalised (n=11), undetermined (n=5). Twenty people have been seizure-free >12-months. Average SERIAS-VAS scores are the same for seizure-free and not seizure-free groups. Longitudinal follow-up will assess SERIAS' ability to detect change in disability relative to change in seizure frequency and treatment regimens over time in individual patients.

Conclusion: SERIAS is a novel epilepsy PROM for clinical trials and practice.

Acknowledgements:
LivaNova USA
Chris Ewart

1520

Do app-based seizure diaries diminish patients' underreporting of epileptic seizures?

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Purpose: Patient-led seizure diaries do not reflect patients' actual seizure activity. Tending to underreport the seizures, often caused by seizure-induced seizure unawareness (Hoppe et al. Arch Neurol. 2007;64(11):1595-1599), patients document only up to 50% of their seizures accurately. However, the introduction of epilepsy health apps has provided a technologically advanced and by patients widely accepted new approach for potentially better seizure documentation. This study aims to explore whether these technological advancements lead to an improvement in seizure documentation.
Method: As part of the SeizeIT2 study, patients at the University Medical Center Freiburg were asked to keep a seizure diary during their stay in the epilepsy monitoring unit. They had the option to choose between a traditional paper format or an epilepsy health app (Helpilepsy). The collected data was retrospectively analyzed, and the documentation performance of both methods were compared using neurologists' Video-EEG annotations as a gold reference by manually assigning the diary entries to the officially annotated seizures. Performance metrics were calculated to assess the outcomes.
Results: Within the SeizeIT2 Freiburg Dataset, a total of 55 patients were included, out of which 18 patients experienced at least one seizure and made at least one seizure diary entry. Among these patients, 8 chose to utilize the app, while 10 preferred the traditional paper form for documenting their seizures. The patients' average sensitivity and F1-score for app-based seizure documentation were higher (77.4% and 82.5%, respectively) compared to traditional paper-based seizure documentation (56.6% and 64.7%, respectively). However, the precision was similar for both methods.
Conclusion: Our findings suggest that app-based seizure diaries have the potential to enhance the performance of patients' seizure documentation. Further studies with larger datasets are necessary to delve deeper into the underlying effects and validate app-based approaches in improving seizure documentation.

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Subjective emotional and cognitive signs of epileptic seizures

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Purpose: We aimed to assess the frequency of emotional and cognitive symptoms during an epileptic seizure among patients with focal or generalized epilepsy
Method: An anonymous cross-sectional survey of epilepsy patients consulted at the tertiary Epilepsy center in Vilnius University Hospital. It consisted of questions on patient demographics, type of epileptic seizures, etiology and subjective emotional and cognitive signs during epileptic seizures; the frequency was rated on a scale from 0% to 100% (0%="never", <25%="rarely", 25-75%="occasionally", >75%="frequently", 100%="always"). Data were analyzed using Microsoft Excel and SPSS 20
Results: The questionnaires of 46 subjects (20 with generalized and 26 with focal epilepsies; 33 (72%) women; mean age 37.74 years;) were analyzed. Of all, 85,4% (92.3% of patients with focal and 80% with generalized epilepsy) reported being aware of all their seizures. The most commonly experienced emotions during a seizure were anxiety or fear (50%, n=23), anger (28%), and sadness (26%), while the rarest ones were joy/pleasure/euphoria (15%, n=7). Of cognitive symptoms, memory impairment was reported at 52%, expressive aphasia - at 41%, déjà vu -at 35%, depersonalization -at 33%, forced thinking, and jamais vu - at 26% each, and streams of thought - at 20% of all patients. The difference between generalized and focal seizure groups was not significant.
Conclusion: The majority of patients with epilepsy (both focal and generalized) experience subjective emotional and cognitive symptoms during their seizures. The most common emotions are anxiety/fear, while the most common cognitive features are memory impairment, expressive aphasia, and déjà vu. Further research is needed on a larger sample of epilepsy patients.

1587

Epilepsy secondary to carbon monoxide poisoning: clinical case and literature review

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Purpose: Highlight a rare etiology of epilepsy.
Method: Clinical case and literature review.
Results: Clinical case: 17-year-old patient with no particularpathological history, victim of accidental CO poisoning, who initially presented psychomotor agitation, the evolution was marked by the appearance of memory disorders and a change in character and personality with epileptic seizures of the stereotype hypermotor type crisis as well as bizarre but also stereotyped movements, & months later, a Para clinical assessment iscarried out in the patient, in particular an encephalic NRI which shows restrictive occipital, frontal and bilateral temporal lesions of hypoxic origin; an electroencephalogram (EEG) with slow rythme initially and generalized epilepsy at 1 year showing a slowed rhythm, with a neurocognitive assessment which objectified an alteration of higher functions.
Conclusion: Through this observation on an update on someneuropsychiatric complications related to CO poisoning, Including epilepsy which remains a rare complication of carbon monoxide poisoning.

1598

Automated detection of convulsive seizures using video recordings with privacy preserving features

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Purpose: Automated seizure detection devices for out-of-hospital epilepsy care are needed. However, current single-purpose and dedicated wearable devices have limitations. Here, we investigated the performance of automated video-based seizure detection approaches that preserve patient privacy.
Method: We analysed convulsive seizures recorded from patients with epilepsy during inpatient video-EEG monitoring admission who had with video and electrocardiogram (ECG) data. Four distinct epochs were identified for each seizure including baseline (60s, ending 240s before seizure onset), pre-ictal (60s, ending at seizure onset), ictal (seizure onset to termination), and post-ictal (300s, starting from seizure termination). We extracted the privacy preserving feature of optical flow, which is a measure of motion, from each video recording. We used two different transformer deep neural networks to analyse features of the video and raw ECG data. Our findings were validated using a five-fold, patient-independent, cross-validation approach.
Results: Forty seizures (35 focal-to-bilateral and 5 generalised tonic-clonic seizures) from 31 patients were included. Using video data alone, the model demonstrated a mean sensitivity of 85% and specificity of 87%; while ECG alone yielded a sensitivity of 97% and specificity of 88% for seizure compared to respective baseline epochs. When video and ECG data were combined, the performance of the model improved to a sensitivity of 95% and specificity of 95%.
Conclusion: We demonstrate high sensitivity and specificity for the automated detection of convulsive seizures using video and ECG.Importantly, the video data was extracted and processed using privacy-preserving methodology. These data can be derived from existing commercially available technology, making them more cost-effective, non-stigmatising to users, and accessible to most patients with epilepsy. Future studies should compare the performance of video-based methods for seizure detection against current non-invasive wearable devices.

1620

Safety and efficacy of fenfluramine in adult patients with Dravet syndrome enrolled de novo in an open-label extension study

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Purpose: To describe safety and efficacy of fenfluramine (FFA) in adult patients (18-35 years old) with Dravet syndrome (DS) who did not participate in the phase 3 clinical trials (NCT02682927, NCT02826863, NCT0296898) but enrolled in the open-label extension (OLE) study de novo.
Method: Demographics, incidence of treatment-emergent adverse events (TEAEs), ratings on the Clin-

ical Global Impression-Improvement (CGI-I) scale, and percent change in monthly convulsive seizure frequency (MCSF) per 28 days were summarized using descriptive statistics. MCSF change from baseline was assessed using the Wilcoxon signed rank test.
Results: Twenty-eight adult patients (15 male, 13 female) enrolled de novo in the OLE. Mean age at enrollment was 25.4 years (range, 19.3-33.3). 26/28 patients experienced at least 1 TEAE; most commonly reported TEAEs were decreased appetite (42.3%), fatigue (19.2%), upper respiratory tract infection (19.2%), nasopharyngitis (15.4%), and somnolence (15.4%). There were no reports of valvular heart disease or pulmonary arterial hypertension. At last visit, investigators and caregivers rated 20/28 and 22/28 patients as 'improved' on CGI-I, respectively. In 17 patients who had both baseline and post-baseline seizure data, a median 50.2% MCSF reduction from baseline over the entire OLE (P<0.001) was reported.
Conclusion: Dravet syndrome is a rare, chronic disorder that persists into adulthood and requires lifelong treatment. In this analysis of adults with DS, there were no new safety signals observed and treatment with FFA was well-tolerated. These data also demonstrate that FFA is effective in adult patients. Further, CGI-I ratings from caregivers and investigators illustrate that adults with DS who are started on FFA are deriving meaningful clinical benefit from treatment. Funded by UCB Pharma.

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Predictors of postoperative epilepsy/seizures in patients readmitted after meningioma resection

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Purpose: Epilepsy/seizures in meningioma patients may occur pre- or postoperatively causing significant morbidity and impaired quality-of-life. Surgical excision is considered a standard management with variable rates of epilepsy/seizure resolution reported after surgery. Employing a national database, we examined the pre- and postoperative incidences of epilepsy/seizures and risk-factors associated with postoperative epilepsy/seizures in patients readmitted within 30-days and/or 90-daysfollowing meningioma resection
Method: The 2010-2014 Nationwide Readmissions Database was analyzed. Consecutive patients undergoing surgery for meningioma resection were identified using appropriate ICD-9-CM codes. Standard descriptive techniques and multivariate regression were used toidentify predictors of postoperative epilepsy/seizure after discharge.
Results: Among 46,107 patients undergoing meningioma resection at index hospitalization, 20.40% (n=9,408) had preoperative epilepsy/seizure diagnosis. The mean patient age was 58.37±13.85 years. Patients with preoperative epilepsy/seizures were more likely to be male (P<0.001), frail (P<0.001), with higher comorbidity-index scores (P<0.001). Overall readmission rate was 30.36%, and was higher among patients with preoperative epilepsy/seizures (36.66% vs. 28.75%, P<0.001). Respectively, 30- and 90-day readmission rates were higher among patients (13.22% vs. 11.73%, P<0.001) and (23.25% vs 20.30%, P=0.04) with epilepsy/seizure diagnosis at index admission. Predictors of postoperative epilepsy/seizures at 30- and 90-day readmissions included the preoperative epilepsy/seizure, malignant meningioma, peritumoral cerebral edema, and higher comorbidity-index scores, while male sex was significant only at 30-day readmissions. Intraoperative electrocorticography was associated with a decreased likelihood of postoperative epilepsy/seizures.
Conclusion: Development of epilepsy/seizures after meningioma resection is likely multifactorial. Identifying factors associated with postoperative epilepsy/seizures after discharge is important in triaging and

closer monitoring of at-risk patients and for adapting management to help improve outcomes.

Basic science

1452

Suppressing microglial cells is a disease modifying intervention for comorbidities in the self-sustained status epilepticus mouse model of mesial temporal lobe epilepsy (MTLE)

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Purpose: Neuroinflammation plays a key in the pathogenesis of epilepsy by driving sustained microglial activation and subsequent neurodegeneration. The role of microglia proliferation and activation in the development of acquired epilepsy is unknown; thus, this study aimed to investigate the effects of microglial depletion immediately following status epilepticus in mesial temporal lobe epilepsy (MTLE) mouse model by measuring the expression of neuroinflammatory markers and characterizing epilepsy severity and neurobehavioral comorbidities of MTLE.
Method: Self-sustained status epilepticus (SSSE) was induced in mice via electrical stimulation. Following termination of SSSE, mice received intraperitoneal injections of a colony-stimulating factor 1 receptor (Csf1R) inhibitor (PLX5622) (50mg/kg ip twice daily), which reversibly depletes microglia, or vehicle injections, for one week. The effects of PLX treatment on gene expression following the SSSE at the time of cessation of PLX treatment was evaluated at acute timepoint. At chronic timepoint, mice underwent neurobehavioral tests and seizure frequency via continuous video electroencephalography monitoring.
Results: At acute timepoint, microglial-mediated depletion significantly downregulated the mRNA expression of proinflammatory cytokines IL-1α (p=0.0013),IL-6 (p= 0.0006), and CD86 (p=0.0002). While in chronic timepoint, PLX-treated mice displayed improved memory, as evidenced by a prolonged time spent in the novel arm of the Y-maze test (p=0.0011) compared to vehicle-treated mice. PLX treatment also reduced depressive behaviour, with significantly lower immobility time on the tail suspension test (p=0.0297) and a trend towards a higher preference for sucrose consumption (p=0.0923) in PLX-treated SSSE animals compared to the vehicle-treated group. However, the results of the treatment intervention did not lead to a significant reduction in seizure frequency.
Conclusion: The differential effects of this intervention on seizures and behavioural alterations suggest that different mechanisms may be responsible for these common sequelae following brain injury. Csf1R inhibition offers a feasible approach to limit neurological dysfunction following epileptogenic insults, offering the potential to improve disease prognosis.

1483

Cardiorespiratory rate down-regulation occurs immediately before and not just during ter-

minal seizures in the Na^+/K^+-ATPase sudden unexpected death in epilepsy (SUDEP) model

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Purpose: Patients with *ATP1A3*-related epilepsy have increased mortality. They are predisposed to apneas and cardiac arrhythmias but mechanisms that specifically lead to SUDEP are unknown. We hypothesized that these involve seizure-triggered terminal apnea, and that significant dysregulation of cardiac and respiratory rates exists not only during but also before seizures occur.

Method: Adult mice (n=7) carrying the most common mutation causing human disease (D801N) underwent stereotaxic EEG intracranial electrode implantation, along with breathing and EKG electrodes in the thoracic muscles. Continuous video-telemetry of these signals was recorded 24 hours/day until terminal events occurred (Spike2 v10, Cambridge Electronics). We determined cause of death and compared cardiorespiratory parameters during baseline-resting, pre-ictal-non-terminal (last seizure before terminal) seizure, and pre-ictal-terminal seizure periods using one-way repeated measures ANOVA with Fisher's LSD post-hoc following normality testing.

Results: All mice eventually had ≥ stage IV terminal seizures and seizure-triggered apnea followed by death. Significant differences were observed in mean R-R wave interval (a measure of the reciprocal of heart rate) ($p=0.017$) and mean inter-breath interval ($p=0.018$) between baseline, pre-ictal-non-terminal seizure, and pre-ictal-terminal seizure periods. Post-hoc analyses revealed significant increases in R-R wave interval and inter-breath interval (both in seconds) between the baseline and the pre-ictal-non-terminal seizure periods (0.114 ± 0.019 vs. 0.196 ± 0.076, $p=0.012$ and 0.423 ± 0.139 vs. 1.016 ± 0.676, $p<0.01$, respectively) and between the baseline and the pre-ictal-terminal seizure periods (0.114 ± 0.019 vs. 0.196 ± 0.061, $p=0.012$ and 0.423 ± 0.139 vs. 0.915 ± 0.545, $p=0.023$, respectively).

Conclusion: In this *ATP1A3* SUDEP model,
(1) there is significant down-regulation of cardiac (bradycardia) and respiratory (bradypnea) rates that occurs before seizures and
(2) death consistently followed seizure-triggered apneas.
This indicates that, at least in this mouse model, SUDEP mechanisms involve significant brainstem and autonomic dysregulation that occurs directly pre-ictally and is exacerbated by the seizure activity that leads to death. This is a novel finding.

1502

Peculiarities of the effect of antiepileptic drugs on seizures in mice with corneal kindling against the background of low-dose premedication Sultiame

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Purpose: To study the effect of an inhibitor of cytochrome P450 enzymes on the severity of the antiepileptic action of the most frequently used AEDs under the conditions of corneal kindling in mice

Method: The study was conducted on white male mice weighing 17-20 g of the BALB/c line, which com-

prised 2 groups of 20 in each. Animals of group 1 (Sultiam line) received intragastrically a 10% aqueous emulsion containing Sultiam 50 mg/kg; animals of group 2 (Control line) received twin emulsion without additives. The introduction of Sultiam (an enzyme inhibitor of the cytochrome P450 system) allows modeling enzyme polymorphisms, which in clinical practice are associated with a decrease in AEDs metabolism. At the same time, corneal electrostimulation (current frequency – 60 Hz, current strength – 3 mA, duration – 3 seconds) was repeatedly provided until the development of a stable generalized kindling syndrome.
The research of the anticonvulsant effect of sultiam, levetiracetam, carbamazepine, valproate, lamotrigine, and retigabine.
The obtained results were statistically processed
Results: All used anticonvulsant drugs showed a reliable anticonvulsant action at the background of multiple prior administration of Sultiam (subeffective dose), however, it was the strongest in the group receiving Sultiam (effective dose, 1.5-1.77 points). The pharmacodynamics of valproate was similar to the pharmacodynamics of sultiam.
Sultiam, suppressing the activity of the cytochrome P450 system, increased the anticonvulsant effect of lamotrigine, despite the fact that, according to research, lamotrigine is not metabolized by CYP450
Conclusion: The results of experimental studies allow to improve the understanding of the mechanisms of interaction of AEDs with their combined use, taking into account individual characteristics, increase the effectiveness and safety of treatment, and also suggest that one of the possible mechanisms of interaction is the modulation of the activity of the enzymes

1543

Patient-derived leucine-rich glioma inactivated 1 (LGI1) protein antibody causes seizures in a passive transfer rodent model

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Purpose: Facio-brachial dystonic seizures, limbic encephalitis and cognitive impairment are seen in patients with autoantibodies to the leucine-rich glioma-inactivated-1 (LGI1) protein. Despite successful modelling of cognitive changes *in vivo*, seizures have not been seen. Using patient cerebrospinal fluid derived LGI1-monoclonal-antibodies (LGI1-mAbs) we developed a passive transfer rodent model to investigate the *in vivo* and *in vitro* electrophysiological effects**.**
Method: Juvenile male Wistar rats were implanted with osmotic pumps (Alzet,USA) containing control antibodies (n=6) or LGI1-mAbs (n=6) for 7-day intracerebroventricular antibody infusion. Wireless EEG transmitters (Opensource Instruments) were used to record EEG from a hippocampal CA3 depth electrode for 21 days. EEG was analysed using automated ictal event detection (Neuroarchiver) and custom code for powerband analysis. Brain slices were used for *in vitro* electrophysiology and immunostaining.
Results: Hippocampal binding of LGI1-mAbs was confirmed on post-mortem immunohistochemistry.

Video-EEG analysis and automated ictal event detection revealed spontaneous epileptic seizures in all 6 LGI-mAb infused rats and none in controls. Two discrete peaks of seizure activity were observed within the 7-day infusion period, with highest seizure frequency on day 2. EEG coastline length was significantly increased in LGI1-mAb animals compared to controls ($p<0.001$). The power in all EEG frequency bands was significantly higher in the LGI1-Mab infused animals ($p<0.01$). Local field potential recordings from day 2 LGI1-mAb injected brain slices (n=21 slices from 8 animals) showed an increase in spontaneous ictal-like spike activity in CA3 region as compared to control slices (n=25 slices from 9 animals; $p=0.01$), and hyperexcitability of CA3 pyramidal cells in whole-cell patch clamp recordings (n=11 cells from 3 animals vs 13 cells from 4 animals; $p<0.05$).
Conclusion: LGI1-Abs are associated with facio-brachial dystonic seizures, tonic-clonic and temporal lobe seizures in affected patients. In this study we have demonstrated the emergence and evolution of seizures during an intracerebroventricular infusion of patient CSF-derived LGI1-mAbs *in vivo*.

1547

Transient seizure clusters and status epilepticus following widespread bilateral hippocampal interneuron ablation

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Purpose: Interneuron loss is a prominent feature of temporal lobe epilepsy in both animals and humans and is hypothesized to be critical for epileptogenesis. As loss occurs concurrently with numerous other potentially pro-epileptogenic changes, however, the impact of interneuron loss in isolation remains unclear. To test the hypothesis that interneuron loss is sufficient to cause epilepsy, we developed a mouse model system to selectively ablate or transiently silence hippocampal interneurons.
Method: *Slc32a1*$^{tm1.1(flpo)Hze}$/J (Vgat-FlpO) mice received bilateral hippocampal injections of AAV9-CAG-frt-DTr to induce diphtheria toxin-receptor (DTr) expression in Vgat-expressing interneurons. In a separate group of mice, the same population was targeted for transient chemogenetic neuronal silencing with DREADDs by injecting AAV9-CAG-frt-hM4D$_i$/HA. Mice were video-EEG monitored 24/7 for one week before treatment with either diphtheria toxin or clozapine-N-oxide (CNO) to mediate interneuron ablation or silencing, respectively.
Results: Interneuron ablation produced dramatic seizure clusters and periods of status epilepticus. Surprisingly, however, after one week seizure activity declined precipitously and status epilepticus events disappeared. Occasional seizures (≈1/day) persisted to the end of the experiment at four weeks. In contrast to the dramatic impact of interneuron ablation, transient silencing produced large numbers of interictal spikes, a significant but modest increase in seizure occurrence and changes in EEG frequency band power. GFAP and Iba1 immunostaining of hippocampal tissue collected from toxin-treated mice at the seizure peak revealed no significant differences between control and ablation groups, suggesting that acute seizures are not driven by inflammation.
Conclusion: Findings demonstrate that abrupt loss or silencing of hippocampal interneurons is sufficient to induce large numbers of acute seizures and spikes. Findings also suggest, however, that the hippocampus is able to regain relative homeostasis approximately one week after ablation, with chronic EEG recordings showing only occasional seizures. Together, the results highlight the importance of interneurons for seizure control, but also demonstrate remarkable homeostatic plasticity.

1551

GLUT1 and cerebral glucose hypometabolism signatures in human focal cortical dysplasia linked to hypermethylation of key glucose regulatory targets

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Purpose: Focal cortical dysplasia (FCD) is a major cause of refractory epilepsy and associated with neurovascular and metabolic dysfunction. The current study examines the regulation of glucose-transporter1 (GLUT1) and brain hypometabolism in FCD patient subtypes that could lead to early diagnosis and intervention.
Method: Studied resected human brain-tissues characterized (n=55) into FCD subtypes. Using methyl-CpG capture with massive parallel-sequencing, DNA methylation analysis was performed on a sample subset (n=14, paired-brain and blood) to determine target-genes linked to GLUT1/glucose metabolism. Brain glucose-lactate levels was measured biochemically, and GLUT1, VEGFα, lactate transporter/MCT2, mTOR by western blot. As "proof-of concept" validation, the effect of a DNA methylation inhibitor, 5-Aza-2'-deoxycytidine (5Aza, 10μM) was tested on [^{3}H]-2-deoxyglucose uptake, GLUT1, VEGFα levels in epileptic endothelial cells (EPI-ECs) and mTOR signaling in HEK cells.
Results: We observe hypermethylation of GLUT1, BDNF and mTOR responsible for glucose metabolism that distinguishes FCD and non-FCD in both the brain and blood samples. Suppressed GLUT1 and low glucose-lactate ratios correspond to elevated VEGFα in FCD2A and FCD2B brain tissues, independent of age/gender. Dysplastic regions with cortical disorganization show GLUT1 suppression compared to non-dysplastic brain tissues and specific-EPI-ECs. Increased mTOR signaling is predominant pathway in dysplastic brains. The DNA methylation inhibitor did not influence cytotoxicity, increased GLUT1 levels (*$p<0.05$) and decreased VEGFα (*$p<0.05$) in EPI-ECs. 5Aza restored glucose uptake (*$p<0.05$) under low glucose-high lactate condition, suggesting DNA methylation influences GLUT1 and cellular glucose-response in EPI-EC, and reduced mTOR and MCT2 levels in HEK.
Conclusion: We propose elevated GLUT1 suppression and hypometabolism are mediated by GLUT1-MCT2-mTOR mechanism in the FCD brain. DNA methylation influences GLUT1, cellular glucose uptake function and mTOR pathways. Furthermore, hypermethylation of GLUT1 and key glucose regulatory genes distinguishes the FCD from non-FCD brain tissue. Together, these studies lead to GLUT1-mediated biomarkers, glucose metabolism and identify early intervention strategies during epileptogenesis in FCD.

1560

Changes and mechanism of NMDAR and synaptic plasticity in anti-NMDAR-GluN1 peptide immunized PTZ-induced epilepsy

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Purpose: The characteristics of NMDAR expression, synaptic ultrastructure, and dendritic spines in anti-NMDAR encephalitis are not well understood
Method: By constructing the GluN 1 peptide-immunized mouse model, the characteristics of NMDAR expression, synaptic ultrastructure, and dendritic spines were explored in mice affected with GluN 1 peptide.
Results: 1, GluN1359-378 mice had spontaneous discharge (76.47%).2, the GluN 1 + PTZ group had shortened seizure latency and increased number of grade IV and V seizures in half an hour.2, GluN 1 + PTZ mice showed no significant change in the hippocampus, while the expression of NR 1 membrane protein was significantly decreased.3, PSD-95 expression was not change in GluN 1 + PTZ hippocampus, and Ephrin B2 and EphB 2 protein expression was significantly decreased.4, the co-localization coefficient between NR 1 and EphB 2 in the GluN 1 + PTZ group.5, decreased synaptic gap width, synaptic postsynaptic dense thickness and active zone length in the GluN 1 + PTZ group. Dendritic spine density of neurons in the GluN 1 + PTZ group
Conclusion: The increased seizure susceptibility in mice immune with GluN 1 peptide; the significant decrease in membrane protein expression of NR 1 and the decrease in EphB 2; the decrease in dendritic spine density in neurons immune with GluN 1 peptide may be related to the decreased expression of NMDAR on the membrane surface and EphB 2 expression.

1566

Clock gene BMAL1 contributes to pharmacoresistance through mTOR pathway in Pentylenetetrazol kindling model of epilepsy

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Purpose: Sleep deprivation induces seizures and increased the risk of drug resistance in epilepsy. However, the mechanism of sleep deprivation in the pharmacoresistance of epilepsy still needs further investigation. In this study, we explored the effect of clock gene BMAL1 on pharmacoresistance in pentylenetetrazol (PTZ) kindling model of epilepsy.
Method: SD rats were divided into habitual group (12:12 light-dark photoperiods) and sleep deprivation group (16: 8 light-dark photoperiods). We established chronic epilepsy model kindled by PTZ and screened pharmacoresistance using phenytoin. Adeno-associated virus (AAV) were used to knockout of BMAL1. The expression of BMAL1, Per2, phospho-S6(P-S6) and P-gp were detected by western blotting and immunohistochemistry.
Results: The expression level of BMAL1 was significantly lower in sleep deprivation group, with overexpression of P-S6 and P-gp, compared to habitual group (all $P < 0.05$). In addition, sleep deprivation increased the rate of pharmacoresistance in PTZ kindling model of epilepsy. Moreover, neuro-specific knockout of BMAL1 significantly increased the rate of pharmacoresistant epilepsy accompanied with overexpression of P-S6 and P-gp (AAV group vs. control group, P=0.023).
Conclusion: Clock gene BMAL1 may contribute to the pharmacoresistance of epilepsy through mTOR pathway.

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The EGFR pathway as novel target for difficult to treat TSC

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Purpose: Tuberous sclerosis complex (TSC) is caused by mutations in *TSC1 / TSC2*, leading to constitutive activation of the mammalian Target of Rapamycin (mTOR) complex 1. Targeted therapy with everolimus was approved for TSC, but fluctuations in success may involve other unknown mechanisms. Recently, caudal late interneuron progenitor (CLIP) cells were identified as common origin of the TSC brain pathologies such as subependymal giant cell astrocytomas (SEGA) and cortical tubers (CT). Further, targeting the epidermal growth factor receptor (EGFR) with afatinib, which is expressed in CLIP cells, reduces cell growth in a cerebral TSC organoid model. However, further investigation of clinical patient-derived data are urgently needed.
Our aim was to observe EGFR expression in SEGA, CT and focal cortical dysplasia (FCD) 2B human brain specimen and to investigate whether a inhibition of its activity could be a potential therapeutic intervention for these patients.
Method: Brain specimens of 23 SEGAs, 6 CTs, 20 FCDs 2B, and 17 healthy controls were analyzed via immunohistochemistry to characterize EGFR expression, cell proliferation (via Ki-67) and mTOR signaling. Protein expression was additionally observed via western blotting. In a cell-based assay using primary patient-derived cells (CT n = 1, FCD2B n = 1 and SEGA n = 4), the effects of afatinib and everolimus on cell proliferation as well as cell viability was observed.
Results: EGFR overexpression was observed in histological sections of SEGA and cortical tuber. Both everolimus and afatinib decreased the proliferation and viability in primary SEGA, tuber and FCD2B cells.
Conclusion: Our study demonstrates that EGFR suppression might be an effective alternative treatment option for SEGAs and tubers, as well as other mTOR-associated malformations of cortical development, including FCD2B.

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Ongoing epileptogenesis in Dravet Syndrome: implications for gene therapy

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Purpose: Heterozygous loss-of-function mutations in the human SCN1A gene, which encodes a subunit of a voltage-gated sodium channel, result in Dravet syndrome (DS), a severe infantile-onset monogenic epileptic encephalopathy characterized by intractable seizures and increased mortality. While the primary genetic deficit triggers the first seizures, repetitive subtle brain injury from recurrent seizures likely results in further epileptogenesis, adding an acquired epilepsy biology is not addressed by gene therapy aimed to restore SCN1A expression. Indeed, there is no indication yet that any gene therapy will lead to seizure freedom in DS. Here we test whether proteins related to glutamate transport and potassium conductance, both depressed in acquired epileptogenesis, are also depressed in DS, and can be considered as therapeutic targets in complement to gene therapy, to achieve seizure freedom in DS.

Method: Adult *Scn1a*$^{+/-}$ mice were monitored for convulsive seizures. Cortical tissue was obtained from heterozygous adult (p>90) seizing and non-seizing *Scn1a*$^{+/-}$ mice and age-matched, wild-type littermate controls (N=6-7/group). Glutamate transporter 1 (GLT-1) and Kv3.1 potassium channel expression was measured by western blot. Statistical comparisons were performed using one-way ANOVA with Tukey post-hoc tests.
Results: GLT-1 protein expression was depressed in seizing DS mice compared to both non-seizing *Scn1a*$^{+/-}$ mutants as well as wildtype (WT) controls (seizing *Scn1a*$^{+/-}$: 80.94±0.11%; non-seizing *Scn1a*$^{+/-}$: 96.60±0.09%; WT: 100.00±0.11%; seizing vs non-seizing: p=0.020; seizing vs WT: p=0.023). Kv3.1 protein was also decreased in seizing DS mice compared to WT controls (seizing Scn1a$^{+/-}$: 95.43±0.11%; non-seizing Scn1a$^{+/-}$: 78.40±0.04 %; seizing vs WT: p=0.013)
Conclusion: Cortical GLT-1 and Kv3.1 expression is reduced in seizing DS mice. These data indicate a progressive acquired epileptic component in DS and underscore the potential for co-administration of gene therapy and targeted pharmacotherapy. Our findings also suggest a role for anti-epileptogenic interventions in DS and other genetic epilepsies.

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Parthenolide ameliorates epileptogenesis, depressive-like behaviour and cognitive dysfunction in kainic acid-induced epileptic mice by inhibiting USP7-mediated NLRP3 deubiquitination

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Purpose: Based on single-cell RNA sequencing, we found that ubiquitin-specific peptidase 7 (USP7) expression is upregulated in the epileptic hippocampus. Using enzymatic screening, we discovered that parthenolide, derived from medicinal herb Feverfew, can specifically inhibits USP7 activity. This study aimed to investigate the role of USP7 and its inhibitor parthenolide on epileptogenesis and epilepsy comorbidities.
Method: Fluorescence localization and protein expression of USP7 in brain tissues of patients without epilepsy and patients with TLE, as well as mice in the sham-operated and KA-induced epilepsy model groups, were examined by immunofluorescence and immunoblotting, respectively. KA-induced epileptic mice received parthenolide treatment (3mg/10ml, i.p.) once daily for 4 weeks. *USP7* knockout mice were generated and then KA-induced epilepsy model was established. The epileptic behavior of the mice was monitored by video, and the hippocampal local field potentials (LFP) of the mice were recorded. The sucrose preference test and the forced swim test were used to detect the depressive-like behavior of mice, and the Morris water maze was used to detected the cognitive dysfunction of mice. Neuronal morphology and apoptosis were detected by Nissl and TUNEL staining. USP7 interacting proteins were identified by co-immunoprecipitation tandem mass spectrometry. Detection of NLRP3 ubiquitination and NLRP3 inflammasome activation in the hippocampus of epileptic mice following *USP7* knockout or parthenolide intervention, and combined hippocampal injection of *NLRP3* overexpression virus.
Results: USP7 is localized in neurons, and its protein expression is increased in the hippocampus of epilepsy. USP7 can immunoprecipitate NLRP3. *USP7* knockout or parthenolide intervention significantly reduced the number of seizures and hippocampal epileptic discharges, improved depressive-like

behavior and cognitive dysfunction, increased NLRP3 ubiquitination, and reduced the protein expression of NLRP3, Caspase-1 p10, IL-1β and IL18, and neuronal damage in the hippocampus of KA-induced epileptic mice.
Conclusion: Parthenolide ameliorates epileptogenesis and neurobehavioral comorbidities by inhibiting USP7-mediated NLRP3 deubiquitination and NLRP3 inflammasome activation.

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Neuroendocrine sensor for sudden unexpected death in epilepsy - prediction and prevention

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Purpose: The overall objective of the NEUROSENSE project is to identify the first SUDEP PREDICTIVE biomarker and develop the first SUDEP predictive and preventive medical device prototype supported by artificial intelligence (AI) that will be able to anticipate life-threatening seizures and trigger an automatic emergency drug administration to prevent SUDEP.
Method: The multiplicity of underlying pathomechanisms and the phenotypical heterogeneity among subjects affected by sudden unexpected death in epilepsy (SUDEP) is the major challenge to its prediction and prevention. As up to now, there is no biomarker nor strategy available to define, predict and prevent SUDEP. There is an unmet medical need to understand the physiology of SUDEP, find a wide-range biomarker within the epilepsy population and devise life-saving prevention.
Results: The results cannot be disclosed at the moment due to IP concerns.
Conclusion: The conclusion is dependent on the results that as mentioned previously cannot be disclosed at the moment due to IP concerns.

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Comparative evaluation of the antiseizure and antioxidative effects of several doses of THC and CBD isolated and in combination

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Purpose: The psychoactive Δ-9-tetrahydrocannabinol (THC) and non-psychoactive cannabidiol (CBD) from *Cannabis sativa* have been studied for treatment of neurological disorders. Here, we compare the antiseizure and antioxidative effects of several doses of CBD and THC alone and in combination.
Method: Adult male Swiss mice were given intragastrically saline or 3, 6, and 10 mg/kg of either CBD, THC or 1.5 and 3 mg/kg of CBD/THC 1:1. Groups were: CBD3, CBD6, CBD10, THC3, THC6, THC10, THC/CBD1.5, THC/CBD3 and Saline. One hour later, animals were given pentylenetetrazol 80 mg/kg i.p.. Latency for the first tonic-clonic seizure and for death were measured. Levels of malondialdehyde (MDA) and nitrite were measured in prefrontal cortex (PFC), hippocampus (H), and striatum (S).
Results: First seizure latency was significantly increased in all treatment groups compared to Saline.

Death latency was significantly increased in CBD6*, CBD10*, THC6**, CBD/THC1.5* and CBD/THC3*** compared to Saline. In PFC, MDA levels were significantly lower in all treatment groups, except CBD3 compared to Saline. Conversely, in H, MDA levels did not differ from Saline in any treatment group, except CBD/THC3*. In S, MDA levels were significantly lower in CBD10**, CBD/THC1.5* and CBD/THC3**. In PFC, nitrite levels were lower in CBD10**, THC6*, THC10**, CBD/THC1.5** and CBD/THC3**. In H, nitrite levels were significantly lower in all treatment groups, except CBD3. In S, nitrite levels were significantly lower in THC3**, THC6**, CBD/THC1.5** and CBD/THC3**.
Conclusion: THC and CBD demonstrated antiseizure effects at all doses tested, increasing the latency to the first seizure and for death. THC and CBD isolated at 10 mg/kg and CBD/THC at both doses decreased nitrite and MDA contents, suggesting antioxidative properties. Importantly, CBD/THC showed superior effects to the isolated compounds, indicating a potential synergism. These results highlight the therapeutic potential of CBD alone and in combination with THC as epilepsy treatment.

Clinical Neurophysiology

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Distribution of postictal slowing has an additional yield to interictal epileptiform discharge in predicting surgical outcomes in temporal lobe epilepsy

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Purpose: To investigate whether bilateral postictal scalp electroencephalography (EEG) slowing activities after focal impaired awareness seizures are associated with poor seizure outcomes after temporal lobe epilepsy (TLE) surgery.
Method: This retrospective cohort study was conducted in the Department of Epileptology, Tohoku University Hospital from 2010 to 2020. The study included 42 patients with TLE who underwent a detailed presurgical evaluation and sequential resective surgery for the unilateral probable epileptogenic temporal lobe with one year or more of follow-up. We reviewed the interictal epileptiform distribution and those of the ictal and postictal epochs of the first focal impaired awareness seizure recorded in presurgical scalp EEG. We classified patients either with postoperative seizure-free status (Engel I) as group A or those with seizure persistence (Engel II-IV) as group B.
Results: Of 42 patients, 29 (69 %) were classified into group A. Compared with group B, group A had a lower number of bilateral postictal polymorphic delta activity (PPDA) (10.3%: 61.5%) and bilateral interictal epileptiform discharges (IEDs) (13.8%: 69.2%) (p=0.003, p=0.001, respectively). A combined analysis of bilateral PPDA and IEDs per individual patient showed significantly more frequent seizure persistence after surgery (p <0.0001) than a single analysis of bilateral IEDs or PPDA alone (p=0.001). The regression analysis revealed that bilaterally distributed PPDA or IEDs had 13.50 or 13.72 times higher odds of persisting seizures within 1 year of surgery (95% confidence interval: 1.90–95.88; 2.12–88.87, respectively) (p=0.009, 0.006).
Conclusion: The results of this study revealed that the bilateral distribution of PPDA was associated with poor postoperative seizure outcomes in patients with TLE, as well as bilateral IEDs. Additionally, the

concomitant bilateral distribution of interictal and postictal changes is a strong indicator of poor surgical outcomes.

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Early EEG may provide better diagnostic yield in children with first unprovoked seizure/s

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Purpose: Electroencephalography (EEG) is an essential tool for evaluating patients with first episode of unprovoked seizure/s (FUS). We compared the yield of abnormalities in early (within 72 hours) vs delayed (2-4 weeks) EEGs in these children.
Method: This prospective observational study enrolled children with FUS consecutively in the age group of 1 month to 18 years. Early EEG was done within 72 hours in 125 children, but delayed EEG after 2-4 weeks could be done in 63 children only due to Covid related restrictions. EEG abnormalities were classified as non-epileptiform (background abnormalities, excess delta activity etc.) or epileptiform (focal or generalized discharges). Impact of clinical factors like age of child, duration of seizure etc. on the diagnostic yield of early and delayed EEGs was studied.
Results: Sixty-three children who underwent both an early and delayed EEG were analysed further. Early EEG showed significantly higher rate of abnormalities in 34 (53.97%), compared to delayed EEG in 23 (36%). Amongst the abnormal early EEGs, 15 (44%) showed epileptiform while 19 (56%) showed non-epileptiform abnormalities. The corresponding figures for delayed EEG were 9 (39%) and 14 (60.9%). The cumulative yield of both EEGs together) was seen in 39 (61%), higher than early or delayed EEG alone. The yield of abnormalities on early EEG was higher (69.23%) if the age of onset of seizure was above 5 years.
Conclusion: In children with FUS, EEG recorded within 72 hours may provide a better yield than delayed EEG after 2 weeks, the yield is higher in children aged more than 5 years. However, half of the abnormalities are non-epileptiform in nature.

1456

Early bedside EEG is a good predictor of cognitive outcome on discharge in children admitted with encephalopathy

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Purpose: EEG monitoring is utilized in neuro-critical care of children with encephalopathy to improve outcomes. We conducted a prospective study to see whether early bedside EEG can predict the cognitive outcome in terms of Mini mental score (MMSE scores) at discharge.
Method: Children aged 3- 18 years admitted in PICU with encephalopathy were enrolled prospectively. They were subjected to EEG within 24 hrs of admission. EEG abnormalities was

classified as- Mild (Focal epileptiform discharges, focal delta), Moderate (GPEDS, high amplitude delta, multifocal ED) and Severe (Low voltage activity non-reactive, Low voltage activity reactive, BS pattern). MMSE scoring was conducted at discharge, scores less than 2 SD below normal for various ages was considered as poor cognitive outcome. Correlation of grade of EEG findings at admission with MMSE scores at discharge was studied.
Results: 55 patients were enrolled- the abnormalities were mild in 31, while 24 children had moderate to severe abnormalities. Electrical seizures were noted in 2 (0.03%). 83.8% of those with mild EEG abnormalities showed good MMSE scores on discharge, while 50% of those with moderate to severe EEG abnormalities at admission showed poor cognitive outcome. There were 11 deaths, out of which 10 showed moderate to severe abnormalities, 8 showed low amplitude background (4 reactive, 4 non-reactive). This difference was statistically significant.
Conclusion: In children admitted with encephalopathy, early bedside EEG done within 24 hours is a good predictor of cognitive outcome at discharge. However, further studies involving larger number of patients is needed for validation.

1492

AI seizure detection in neonates

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Purpose: Seizure incidence in the neonatal period is higher than any point in life. As recognition is based on often subtle stereotypical movement observation, improving identification in real time for prompt treatment initiation is crucial. Currently for in-patient settings, the gold standard of long-term video EEG typically necessitates technician teams with physician supervision/review. Time-consuming and error-prone, seizures are often missed altogether. A lack of trained neonatal specialists to collect, monitor and review video EEG has been a barrier to improved neonatal seizure care. An innovative solution is artificial intelligence to identify seizures in EEG data.
Method: ML model was pre-trained using data from a public online data repository (Stevenson et al., 2019) containing EEG from 73 NICU patients. The EEG was collected using the International 10-20 system with a 19-channel montage and sampled at 256 Hz, digitally band-pass filtered from 0.5 to 40 Hz offline, and resampled at 128 Hz. Based on our prior research, seizure and non-seizure clips were then re-clipped to four second clips for classification. The ML model was built in Python 3.9 and the Tensorflow-GPU platform and trained using a dual GPU (NVIDIA Quadro RTX 8000)

system. The model architecture was a fully convolutional neural network with 29,274 trainable parameters. The pre-trained model was then used to train a model using 10 patients from the NICU at Dell Children's Medical Center. The model was trained for 500 epochs.
Results: The model was tested against patients not included in the training data. The trained model had a maximum sensitivity of .99 and specificity of .89, showing that high accuracy can be achieved in the detection of neonatal seizures. The Receiver Operator Characteristic (ROC) curve showed high sensitivity was attained with low false positive rates.
Conclusion: The results demonstrate the feasibility of training AI models to identify seizures in a NICU setting.

1539

Diminished circadian and ultradian rhythms of brain activity in pathological brain tissue in human epilepsy

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Purpose: Modulatory biorhythms have long been associated with epilepsy, and this association is bi-directional. Multiple mechanisms are thought to underpin these associations; but functionally, in humans, little is known about their expression in the brain or their interaction with epilepsy. Specifically, although multiple biorhythms are recorded in ongoing brain activity, we currently do not know if these biorhythms are functionally altered in pathological tissue.
Method: We used continuous intracranial EEG recordings over multiple days in 39 people with focal refractory epilepsy. We extracted biorhythms of neural activity on circadian and ultradian timescales in simple signal properties such as band power. We analysed if these biorhythms varied in the presence of pathology.
Results: Circadian and multiple ultradian rhythms were diminished in magnitude in regions that were deemed to be pathological compared to healthy tissue (median AUC>0.7, $p<0.05$ across subjects). This effect was persistent in time in most patients in circadian and multiple ultradian rhythms, independent of seizure occurrence.
Conclusion: To our knowledge, our findings provide the first evidence that brain pathology is functionally associated with diminished biorhythms in human epilepsy independent of seizure occurrence. Future work will investigate the causal mecha-

nisms underpinning our findings and may allow for novel therapies leveraging these biorhythms.

1569

Using fully connected layer to extract interpretable component for electroencephalogram classification: a clinical application of convolutional neural network

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Purpose: Convolutional neural network (CNN) is a specific type of deep neural network that works based on an end-to-end training strategy. The methods for CNN interpretation remain limited for electroencephalogram (EEG) data. Herein, we evaluate the intelligibility of the fully connected layer (FCL) in CNN learning.
Method: The proposed neural network comprises a novel FCL block, which allows CNN to extract task-related interpretable spectrum. To guarantee that the CNN will learn task-related frequencies rather than noise, we used Bonn dataset and choose 2 tasks (task 1: open eyes v.s. closed eyes, task 2: interictal stage v.s. ictal stage) with well-known neurophysiological characteristics for evaluation. The initial weights of the neurons in the hidden layer are set to ensure a uniformly distributed power spectral density. After training, task-related spectral features are enhanced in these neurons.
Results: The overall accuracy of using this proposed CNN model was 75.3% and 85.1% for task 1 and task 2 respectively. To take into account that evaluating the classification based on per EEG segment may spoil the overall evaluation procedure, we re-evaluated the performance on a sample-level. In this case, we achieved an overall accuracy of 95.5% in task 1, and an overall accuracy of 92.0% in task 2. Spectral analysis showed that task-related features were enhanced in FCL. Specifically, we showed that the enhanced spectral features of FCL was in alpha band in task 1, which was largely in agreement with the physiological reactivity of posterior rhythm when eyes closed. Analogously, FCL intuitively presented the changes in theta activities when CNN was employed to recognize the ictal stage.
Conclusion: The proposed CNN is unique in extracting EEG spectral features using FCL and may extend the clinical application of AI-assisted EEG classification and interpretation.

1590

Optimized seizure forecasting with wearable devices using multi-day cycles and acute machine learning

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Purpose: The unpredictability of seizures can be debilitating and dangerous for people with epilepsy. Accurate seizure forecasters could improve quality of life for people with epilepsy but must be practical for long-term use. Here we demonstrate pseudo-prospective forecasts with non-invasive peripheral wearable devices with seizure confirmation from concurrent chronic EEG recordings.
Method: Patients were recruited for ultra-long-term monitoring with a wearable device (Empatica E4/ Fitbit Inspire HR or Fitbit Charge 3) and concurrent chronic EEG monitoring (UNEEG SubQ, NeuroPace RNS or Medtronic Summit RC + S) at Mayo Clinic, Rochester MN and King's College London. Physiological data was recorded from enrolled patients for at least six months. EEG data was reviewed, and seizures were confirmed by neurophysiologists. Wearable device recorded step counts and heart rate signals were used to train two forecasting algorithms; short-term memory (LSTM) recurrent neural network and a cycles-based models. Final forecasts were an ensemble of those classifiers, which combined short (minutes to hours) and long (days to months) horizons.
Results: Ten participants with epilepsy were included in the forecasting analysis. An average of 311 days of wearable monitoring and 65 seizures were recorded per patient. LSTM forecasts performed better than chance ($p<0.05$) for 8 of 10 participants, with an average AUC score of 0.67 and AUC of 0.63 across all subjects. Cycles-based forecasts performed better than chance for 7 of 10 participants, with an average AUC score of 0.64 across all subjects. The ensembled forecast model improved forecast scores for 3 participants.
Conclusion: This study demonstrated the feasibility of forecasting electrographic seizures with wearable devices and the possibility to enhance the performance using an

ensemble model which is the combination of two established forecasting techniques: LSTM models for short horizon (minutes to hours) forecasting and cycles-based models for long horizon (days to weeks) forecasting.

1604

Can a single machine learning classifier pipeline detect seizures in two different patient datasets?

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Purpose: Recently, data science techniques have advanced significantly, opening the possibility to achieve accurate detection of seizures in electroencephalogram (EEG) signals (Karoly PL et al. Nat Rev Neurol. 2021;17(5):267-284). However, studies are yet to identify an automated classification approach able to effectively identify seizures in multiple datasets without dataset-specific preprocessing. Such an approach would make clinical diagnosis simpler and less labour-intensive. Here, we address this by testing diverse pipelines for feature selection and seizure classification in two datasets with different characteristics.
Method: We implemented two models based on different principles of machine learning, Logistic Regression and XGBoost, to detect seizures in two publicly available datasets, Temple University Seizure Corpus (TUSZ, 675 subjects, 4 montages, 1476 hours of recording) and Children's Hospital Boston (CHB-MIT, 24 paediatric subjects, 916 hours of recording). To ensure that the detectors were universal, no dataset-specific filtering was applied. We calculated 40 unique temporal and frequency features for each available EEG channel (Vanabelle P *et al*. J Biomed Res. 2019; 30;34(3):228-239, Hristova *et al.* Brain. 2021;144(5):1576-1589). Each model was tested with a full and reduced set of features obtained with the Boruta feature selection method (Kursa MB *et al*. Journal of Statistical Software 2010;36(11), 1–13.).
Results: We obtained an average receiver operating characteristic curve (AUC) result of 0.72 for XGBoost in both datasets. Logistic regression achieved a result of 0.74. After feature selection, models yield 0.72 and 0.76 for XGBoost and logistic regression, respectively.

Conclusion: The logistic regression model gave better results in terms of AUC, however, XGBoost returned more stable and balanced results across various metrics. The results suggest that a single seizure detection based on appropriate feature selection and classifiers can achieve stable seizure detection performance across two datasets with different characteristics. Further investigation is ongoing into the reliable and comprehensive seizure detection method across multiple datasets.

1613

Analysis of clinical Features and EEG characteristics of critically Ill anti-NMDA receptor encephalitis

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Purpose: Analyzing the characteristics of routine EEG and quantitative EEG for early identification of critically ill anti-NMDA receptor encephalitis.
Method: The patients who were hospitalized and diagnosed in the First Affiliated Hospital of Guangxi Medical University were retrospectively analyzed as a case group. Equally matched healthy subjects were taken as healthy control group; case group was divided into critically ill and non-critically ill group. Analyzing routine EEG indicators, quantitative EEG indicators (RBP and β/δ power ratio) to summarize the EEG characteristics.
Results: (1) 88 patients were included , including 31 patients in the critically ill group, 57 patients in the non-critically ill group.(2) Compared with the non-critically ill group, the critically ill group had fever (64.52% vs 33.33%), status epilepticus (70.68% vs 36.84%), speech disorder (64.52% vs 36.42%), involuntary movement (61.29% vs 10.53) %), coma (70.97% vs 12.28%), and central hypoventilation (70.97% vs 3.51%) were more common (P<0.05). In the critically ill group, more proportions required mechanical ventilation (70.97% vs 3.51%), tracheotomy (48.39% vs 3.51%), more pneumonia (96.77% vs 70.17%), increased cerebrospinal fluid pressure (58.06% vs 28.07%) (P<0.05). (3) Compared with the non-critically ill group, the critically ill group showed a higher percentage of abnormal EEG on routine EEG (67.74% vs 35.09%), diffuse slow waves were more common (90.32% vs 52.63%), the proportion of delta brush waves appeared was higher (54.84% vs 28.07%), (P<0.05). (4) RBP-δ increased more

obviously in critically ill group, and RBP-α1, RBP-β1, β/δ power decreased more obviously. **Conclusion**: (1) The routine EEG of critically ill anti-NMDA receptor encephalitis showed a higher proportion of highly abnormal, and diffuse slow waves and delta brush waves were more common. (2) The RBP-δ of critically ill anti-NMDA receptor encephalitis increased, and the power ratio of RBP-α1, RBP-β1, and β/δ power ratio decreased more obviously, which may be a good indicator for differentiating groups.

1634

Paroxysmal depolarization shift - is it an interictal phenomenon in humans?

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Purpose: Cellular correlates of epilepsies had been identified as large intracellular depolarizations and identified as paroxysmal depolarization shifts (PDS). It has been studied in detail in acute and subacute epilepsy models in animals, and they corresponded to the experimental analogue of interictal epileptiform discharges (IED). One of the most defining characteristics of PDS is the involvement of multiple neurons into an excessive firing burst within a circumscribed area of the brain, where sudden disruption of the inhibition may occur. Intracerebral microelectrode measurements in humans demonstrated rather variable neuronal discharge patterns during IEDs, even in the seizure initiation zone.
Method: Eight drug resistant epilepsy patients implanted with intracortical micro-electrodes were involved in this study to analyze the excessive neuronal discharge patterns. Different spontaneous behavioral states and electrical stimulation events performed during the clinical mapping paradigms were included such as single pulse stimulation evoked cortico-cortical potentials (CCEP), and high frequency induced after-discharges (AD). Loss of regulatory influence characteristic to the abruption of inhibition was characterized by entropy measures.
Results: Based on literature data PDS reflects large EPSP with excessive neuronal firing throughout the cortex, harboring temporal disruption of inhibition. PDS in the original animal models can also be considered rather as ictal event. In humans, IEDs in focal epilepsy are heterogeneous and may show low/near normal level of excitation. A subset of interictal events, like spike and wave discharges in generalized epilepsy, intrahippocampal IEDs, CCEP and AD events seems to showed excessively increased neuronal firing along with ictal events that harbored the vast majority of pathologically elevated firing in humans.
Conclusion: Although PDS (occasional, sudden, excessive discharge of grey matter) has been considered the hallmark epiphenon of epilepsy, its usefulness in diagnostics with microelectrodes, is still before clinical tests, after more than 50 years.

Comorbidities

1466

Epileptic seizures in patients with multiple sclerosis

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Purpose: The aim of investigation was to study the characteristics of epileptic seizures in MS patients. The study was conducted in the Baku (the capital of the Republic of Azerbaijan) as part of the national program for the study of MS, in the period 2013-2020.
Method: The study material included 559 patients with proven MS - 392 (70%) female patients, 167 (30%) male. MS was diagnosed according to the 2010 McDonald criteria.
Results: Of the 559 patients with MS, 7 had epileptic seizures (1.25%) - 6 women (85.7%) and 1 man (14.3%). None of the patients were found to have other risk factors for epilepsy, such as brain trauma, cerebral ischemia, drug abuse, etc.
In 1 patient, epilepsy manifested before the clinical manifestations of MS, in 6 during treatment. In 3 out of 7 patients, seizures met the criteria for epilepsy (0.53%). All patients had pathological changes on the EEG.
In 3 patients, the first epileptic seizures occurred during treatment with disease-modifying therapies (DMTs). Discontinuation of the treatment led to a reduction in seizures in only one patient. Four patients had focal seizures with bilateral tonic-clonic generalization. 3 patients showed generalized seizures with unknown onset. None of the patients had status epilepticus.
5 patients took carbamazepine for a long time and one patient took valproic acid.
Conclusion: The study of the prevalence of epileptic seizures in patients with MS showed their rather rare occurrence. The most frequently recorded focal seizures point to the role of brain damage in MS in the implementation of epileptic seizures.

1563

White matter brain-age in diverse forms of epilepsy and interictal psychosis

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Purpose: While brain aging in epilepsy has been attracting attentions recently, brain-age

based on white matter microstructures is less investigated. Given the brain network dysfunction in epilepsy, the white matter tracts, which primarily interconnect various brain regions, could be of special importance. In the current study, we focused on the white matter brain aging in diverse forms of epilepsy as well as comorbid psychosis.
Method: We obtained brain diffusion tensor imaging (DTI) data at 3T-MRI in 257 patients with epilepsy and 429 healthy subjects. DTI data were processed with tract-based spatial statistics and mean fractional anisotropy (FA) values within the JHU white-matter tractography atlas were calculated. Thereafter, the ROI-based FA values of the healthy subjects were utilized to build a brain-age prediction model, and we calculated the brain-predicted age difference (brain-PAD: predicted age – chronological age) of patients and healthy controls.
Results: Almost all epilepsy categories showed significantly increased brain-PAD ($p<0.001$), including temporal lobe epilepsy (TLE) with no MRI-lesion (+4.26yr), TLE with hippocampal sclerosis (+9.07yr), extratemporal focal epilepsy (+5.46yr), epileptic encephalopathy (+18.9yr), except for idiopathic generalized epilepsy (IGE). Patients with psychogenic non-epileptic seizures also presented increased brain-PAD (+12.6yr). In TLE, interictal psychosis significantly raised the brain-PAD by 8.7 years.
Conclusion: We observed increased brain aging in most types of epilepsy except for IGE. White matter aging in epilepsy was mostly consistent with that of gray matter aging finding in the previous studies. These findings may suggest abnormal aging mechanisms in epilepsy and comorbid psychotic symptoms.

1571
Cognitive status in patients with temporal lobe epilepsy

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Purpose: Temporal lobe epilepsy (TLE) is a chronic neurological disorder that can occur alongside cognitive changes, which affects multiple cognitive domains.
Objective: To evaluate the cognitive performance of patients with TLE using the Montreal Cognitive Assessment (MoCA) and analyze the sociodemographic and clinical factors of influence.
Method: Data were collected from forty TLE patients during a neurological consultation through a suitable questionnaire designed for this study and assessed using the test (MoCA).
Results: This study showed that the overall mean score for MoCA was 18.88 (8.17). The main altered subtests concerned memory recall, executive functions, Verbal fluency, and attention. There is a strong correlation ($r = 0.600$, $P = 0.000$) between higher MoCA scores and a higher number of years of education. Besides, the correlation between lower MoCA scores and the

highest number of therapy (r = -0.340, P-value < 0.05) and the highest number of years with seizures (r = -0.343, P < 0.05) and higher seizure frequency (r = -0.345, P-value < 0.05) were also significant.
Conclusion: The (MoCA) has proven its relevance for screening cognitive deficits in several domains in this sample of TLE patients. The regular diagnosis of cognitive disorders and their influencing factors in epileptic patients is necessary for better management

1577

Epileptic seizure as the first symptom of brain tumor

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Purpose: We present a single-center retrospective cohort study of patients operated on for brain tumors at Vilnius University Hospital between 2015 and 2020 to assess epileptic seizures as the first symptom of a tumor.
Method: We analyzed consecutive (n = 1039) patients who underwent craniotomy for the indication of brain tumor confirmed by postoperative pathology. Patients who experienced epileptic seizure as the first symptom of tumors were analyzed versus those who experienced any other symptoms before the diagnosis. Key results were summarized as odds ratios for the risk of seizures across tumor types, grades, and locations.
Results: From 696 operated patients, seizure as the first symptom of brain tumor was in 164 patients (23.56%). Patients who experienced seizures were 5.88±2.75 years younger, they earlier received brain MRI and brain surgery. Seizures were significantly more often the first symptom of a tumor in the frontotemporal (OR=1.65, p=0.050) and temporoparietal (OD=1.50, p=0.036) lobes compared to the occipital lobe (OR=0.37, <0.001). Grade II and III tumors had a significantly higher risk for seizures OR=3.93 (p<0.001) and OR=2.76 (p=0.012) respectively. Seizures were more likely to occur with oligodendroglioma, diffuse astrocytoma, anaplastic oligodendroglioma compared to glioblastoma, meningioma, and metastases. A small number of patients had DNET, fibrillary astrocytoma, and ganglioglioma, however, they always had seizures. 87 patients experienced post-operative seizures, with a risk 5.5 times higher in those with pre-operative seizures. Median follow-up was 7.62±0.23 months with the first seizure occurring at 3.43±0.17 months.
Conclusion: One in four brain tumors manifests with seizures as the first symptom. Certain tumor types have a higher risk of seizures. Preoperative seizures are linked to earlier diagnosis and treatment. Postoperative seizure risk is significantly higher in patients with preoperative seizures.

1594

Long-term neurocognitive and cortical network dysfunction following mild trau-

matic brain injuries

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Purpose: Mild traumatic brain injuries (mTBIs), also known as concussions, are common in high-impact sports like ice hockey and American football. Concussions have been linked to long-term changes in cortical networks and neurocognitive dysfunction. As such, repetitive mTBI may increase the chance of developing Post-Traumatic Epilepsy (PTE) later in life. No credible biomarker exists at this time to identify individuals who will develop long-term complications following mTBI, including PTE. Here, we explored diagnostic and predictive biomarkers for delayed TBI complications in rats.
Method: Male rats aged 8-10 weeks-old received five consecutive mTBIs using a weight drop model. Acute neurological scores were collected 24hrs after each impact. Elevated plus maze, Sucrose preference and novel object recognition cognitive tests were used at 3-4 weeks and six months post-TBI to test anxiety, depression, and short-term, and spatial memory respectively. Rats were implanted with EEG electrodes and recorded at four weeks and six months post-TBI.
Results: Animals exposed to mTBIs showed increased anxiety and impaired short-term and spatial memory at 3-4 weeks and six months post-TBIs. Neurological scoring collected early following repeated mild TBI predicted delayed cognitive impairments at 3-4 weeks and six months. Recurrent epileptic seizures (SLEs) were recorded in thirty percent of TBI animals at four weeks post-TBI, and in sixty percent at six months ($p=0.004$). At six months, epileptic animals showed declined memory performance compared to TBI animals with no epilepsy ($p=0.02$). Aside from seizures, an abnormal intermittent EEG slowing (AKA paroxysmal slow wave events) significantly separated the epileptic animals from no PTE or sham controls (AUC 0.87, $p=0.001$).
Conclusion: We demonstrate diagnostic and prognostic biomarkers for long-term neurocognitive decline and post-traumatic epilepsy. Our findings offer new avenues for diagnosing epileptogenesis and monitoring anti-epileptogenic treatment following mTBI.

1618

Epilepsy and Ramadan: about 120 cases

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Purpose: This study aims to assess the effect of Ramadan fasting on seizure control and to determine factors that could affect the seizure freedom of patients with epilepsy (PWE).

Method: A case series study was conducted between April 24 and May 22, 2023. A structured, standardized questionnaire was applied to the volunteers participating in the study. All volunteers are over the age of 18.
The survey was distributed through PWE WhatsApp local groups and completed by neurologists during consultations. We collected information on disease duration, seizure type, and frequency, antiepileptic drugs (AEDs), worsening of the disease during Ramadan, and causes of the worsening. Statistical analysis was done using SPSS 23.0. Informed consent was obtained.
Results: We report a case series of 120 patients, 50 males, and 70 females, with a sex ratio of 1.4. 93% of patients were adults under 50 years old. The seizure type was focal in 25%, focal with bilateral generalization in 45.8, and generalized in 29.2%. The median duration of illness was 14 years, with a minimum of 1 year and a maximum of 50 years.
51.7% of our patients reported a worsening of the disease during Ramadan. The most common causes of the aggravation reported were lack of sleep in 32.5% and sleep fragmentation in 20%. The mean sleep duration was 8.23+/-1.46. Attitudes towards worsening were to stop fasting in 62.5% and contact the doctor in 30.8%.
80% of patients who changed their drug regimen experienced worsening of their disease against 44% of PWE who didn't change their drug regimen (p=0.001).
Conclusion: This study assumes that Ramadan fasting could aggravate epilepsy, especially in patients who have just changed their treatment regimen. Future research on risk factors of seizure worsening will allow the development of specific guidelines to guide clinical practice.

Drug Therapy

1439

Cerliponase alfa for the treatment of CLN2 disease in a patient cohort including children < 3 years old

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Purpose: Open-label studies in children 3 to 16 years of age with CLN2 disease showed that biweekly intracerebroventricular (ICV) infusion of 300 mg cerliponase alfa slowed deterioration in motor and language function. We report findings from a study to assess safety and efficacy of cerliponase alfa in an expanded cohort including children <3 years.
Method: Subjects received ICV cerliponase alfa biweekly; dosage was based on age (subjects

≤2 years receive <300 mg). Safety was assessed by adverse event (AE) frequency. The primary efficacy endpoint was rate of decline in score on the motor and language (ML) domains of the CLN2 Clinical Rating Scale, comparing treated subjects with matched historical controls.
Results: A total of 14 subjects were enrolled (8 female, 6 male). Mean (SD) baseline ML score was 4.6 (1.7); mean (SD) age at baseline was 3.1 (1.5) years (range: 1.1-6.0). Subjects received cerliponase alfa for a mean (SD) of 140.4 (6.0) weeks. Twelve subjects were matched to historical controls: mean (SD) rate of decline in ML score was 0.15 (0.24) points/48 weeks for treated subjects and 1.30 (0.86) points/48 weeks for matched controls (mean difference: 1.15; 95% CI: 0.80, 1.50). Among treated subjects <3 years of age at baseline (n=8), 7 subjects had a baseline ML score of 6 and remained at an ML score of 6 at end of study. All subjects experienced ≥1 AE; the most common drug-related AEs were pyrexia and hypersensitivity. Twelve subjects experienced ≥1 serious AE; there were no deaths or discontinuations due to AEs.
Conclusion: ICV-administered cerliponase alfa slowed the decline in motor and language function in children with CLN2 disease, including those <3 years of age, with a safety profile consistent with prior studies. Additionally, these results may suggest that early initiation of treatment can delay symptom onset.
Funding: BioMarin Pharmaceutical Inc.

1459

Long-term efficacy of adjunctive cenobamate in patients with refractory epilepsy – a Polish experience

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Purpose: To evaluate long-term efficacy, safety, and tolerability of adjunctive cenobamate (CNB) in patients who continued treatment after completing an open-label extension (OLE) of the randomized, double-blind, placebo-controlled study. CNB was not reimbursed in Poland until March 2023.
Method: Patients with uncontrolled focal seizures despite treatment with 1–3 antiseizure medications who completed the 18-week double-blind study could enter the OLE, where they underwent a 2-week blinded conversion to CNB (target dose, 300 mg/d; min/max, 50/400 mg/d). Patients who completed the OLE (39) were offered the opportunity of continuing on CNB.
Results: Thirty eight patients (18; 47.3% females) continued on CNB after completion of the OLE. The median age of patients at the beginning of therapy with CNB was 39,3 years (18-57) years. The mean duration of epilepsy before entering the double blind study was 15.0 years

(range 4–34 years) and the mean seizure frequency per month was 8 (4-20). As of May 2023, the median (range) duration of CNB exposure was 96 (1.1–68.7) months. Retention rates since the completing the OLE was 100%, At the end of observation the mean dose of CNB was 201 mg (50-350mg) and the mean seizure frequency per month was 3 (0-8). Twenty four patients (63,1%) achieved ≥50% seizure reduction and 8 (21%) has been seizure free for at least six months. Similar to the other studies, adverse events included dizziness, somnolence, and headache.
Conclusion: Long-term efficacy, including 100% and ≥50% seizure reduction, was sustained during 96 months of CNB treatment. No new safety issues were identified. These results support the potential long-term clinical benefit of cenobamate

1464
Perampanel as early treatment for epilepsy and sleep-related seizures

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Purpose: This study aims to evaluate the real-world effectiveness and safety of perampanel as an early treatment for epilepsy patients, especially those with sleep-related seizures.
Method: A retrospective, observational study enrolled patients aged ≥15 years with a diagnosis of focal or generalized epilepsy receiving perampanel. Efficacy, tolerability, and safety assessments were performed every 3 months for 6-12 months. Patients were divided into early(mono or first add-on) and late(second or later add-on) groups in the course of their treatment. A comparative analysis was also conducted for a subgroup of patients with seizures that predominantly or exclusively manifest during sleep.
Results: Perampanel demonstrated a favorable efficacy and safety profile for treating focal or generalized epilepsy with a dose of 2 to 6 mg/day. The seizure reductions of 75% and 100% were significantly higher in the early (n=36) than late (n=39) treatment group at 6 months (84.6% vs. 42.3%, p=0.004; 61.5% vs. 11.5%, p=0.001) and at 12 months (88.2% vs 42.1%, p=0.011; 52.9% vs. 10.5, p=0.017). Among patients with sleep-related seizures, the rates of 75% and 100% response were also higher in the early (n=27) compared to the late (n=11) group at 12 months (82.3% vs. 44.4%, p=0.023; 53.8% vs. 11.1%, p=0.074). The retention rate was higher in patients with sleep-related seizures (n=38) than in the overall population (n=75), even in the late add-on treatment at 12 months (65.0%, 81.8% vs. 59.3%, 54.5% in the early and late groups, respectively). Treatment-emergent adverse events (n=92) were generally mild or moderate, with nervous system disorders such as dizziness (12.0%), gait disturbance (12.0%), and somnolence (9.8%) being the most frequently reported.
Conclusion: Perampanel was effective and well-tolerated as a mono or first add-on treatment for epilepsy patients, particularly those with sleep-related seizures. Close attention should be

given to the risk of falls and suicide attempts when using perampanel.

1475

Status epilepticus in patient with Lennox Gastaut syndrome caused by drug withdrawal due to wrong diagnosis of DRESS syndrome

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Purpose: To rise awareness among neurologist regarding DRESS syndrome, considering drug withdrawal in mistakenly diagnosed patient could be life threatening.
Method: We report a case of 20 years old male patient, who has been diagnosed with Lennox Gastatut and severe mental retardation syndrome since childhood. For the last 15 years the patient has been receiving the following antiseizure medications (ASM): phenobarbital 100mg a day, lamotrigine 100mg bid and sodium valproate 500mg bid. Despite the treatment, patient was having seizures on daily basis, with varying frequency. Patient was bedridden and mother was a solely caregiver. During her daily care routine, she noticed a rash on his trunk and the following day she had noticed a spread of above mentioned rush on his arms, legs and back. Patient did not have any fever nor any other systemic symptom. Mother took him to a private practice neurologist who discontinued all of the above ASM, and introduced levetiracetam, thinking that patient had developed dress syndrome (drug reaction with eosinophilia and systemic symptoms). Patient had severe seizure worsening and eventually developed status epilepticus, and was admitted to neurological intensive care unit (ICU). The seizures ceased after phenobarbital loading dose, but urinary tract infection developed contributing to his prolonged stay in the ICU.
Results: Extensive work up has been done in order to confirm that patient indeed had Dress syndrome. Eventually, the diagnosis of pityriasis rosea was made. ASM were introduced again, with slight dose correction.
Conclusion: Understanding the pathophysiology behind THE dress syndrome, it's clinical presentation and criteria is crucial for adequate diagnosis. Both, unrecongised as well as misrecognised diagnosis, lead to treatment delay with severe consequences.

1476

Which psychogenic non-epileptic seizures (PNES) patients are more likely to be treated with anti-seizure medications?

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Purpose: To determine the risk factors for misdiagnosis of Psychogenic Non-Epileptic Seizures (PNES) as epilepsy.
Method: The medical records of patients that underwent video-electroencephalogram (EEG) monitoring were reviewed retrospectively. Patients that had PNES without epileptic seizures (ES) were included in this study. Baseline personal and monitoring characteristics were collected. The patients were then divided into two groups based on their therapeutic status. Patients in the treatment group were again divided into two groups based on the number of anti-seizure medications (ASM) they were treated with.
Results: Fifty-seven patients diagnosed with PNES were included in this study. Thirty-seven patients were under treatment and 20 patients weren't under treatment at the time of monitoring. Convulsive seizures, abnormal interictal EEG patterns, and pathological brain imaging findings were more frequent among patients in the treatment group ($p<0.05$). Patients with convulsive seizures were more likely to be treated with multiple ASM in comparison to patients with only dialeptic seizures ($p<0.05$). Lastly, patients in the treatment group were monitored longer and had fewer seizures during monitoring ($p<0.05$).
Conclusion: PNES patients with abnormal EEG patterns and pathological brain imaging findings are more likely to be treated with ASM. Pure dialeptic nature of seizures is less likely to be misdiagnosed as ES. In addition, patients with such seizures are less likely to be treated with multiple treatment lines.

1478

Corticosteroids vs clobazam in epileptic encephalopathy with spike wave activation in sleep; results of the RESCUE ESES trial

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Purpose: Epileptic encephalopathy with spike wave activation in sleep (EE-SWAS) is associated with acquired cognitive and behavioural deficits. This European multicentre randomised controlled trial aimed to compare efficacy of treatment with corticosteroids and clobazam after six months on cognition, in 130 patients.
Method: Patients were eligible if they were 2-12 years, diagnosed within 6 months prior to inclusion and had not been treated with clobazam or corticosteroids. Patients were randomly allocated to oral clobazam (range 0.5-1.2 mg/kg/day) or corticosteroids (either 1-2mg/kg/

day orally or 20mg/kg/day intravenously for 3 days every 4 weeks). Primary outcome was cognitive function after 6 months, assessed by 1) responder rate (improvement of ≥11.25 IQ-points), 2) change in total IQ and 3) change in cognitive sum score (Z-score based on 6 cognitive domains). Secondary outcomes were SWAS index, incidence of seizures and safety. Data was analysed by the intention-to-treat principle. Linear regression analysis was used to determine prognostic factors for treatment effect.
Results: Between 2012 and 2022, 22 patients were included in the corticosteroid arm and 23 in the clobazam arm. The trial was terminated prematurely for feasibility reasons. Responder rate was 5/20 in the corticosteroid group versus none in the clobazam group (OR 13.1, CI 1.3 – 1775.0, p=0.0248). Mean delta total IQ was higher in the corticosteroid group (β 5.6, CI 0.3 –10.8, p=0.0386). The difference in mean cognitive sum score was 0.2 (CI -0.1 – 0.4, p=0.2045). Secondary endpoints did not differ between the two treatments. Besides treatment with corticosteroids, having an unknown etiology was significantly predictive of a higher delta IQ (β 7.5, CI 2.6 – 12.5, p=0.004). This effect sustained in a multivariate analysis (adjusted R^2 0.265, p=0.0020).
Conclusion: Although the trial was prematurely terminated, results of 45 included children revealed significantly higher responder rate and IQ increase, suggesting superiority of initial treatment with corticosteroids in children with EE-SWAS.

1486

Real-world data on the use of cannabidiol in patients with Lennox-Gastaut Syndrome or Dravet Syndrome in the UK early access programme

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Purpose: We retrospectively evaluated clinical outcomes of patients with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) treated with plant-derived highly purified cannabidiol medicine (CBD; Epidyolex®; 100 mg/mL oral solution; GW Pharma [International] B.V.) in an Early Access Programme in two UK centres.
Method: Patients aged 2–17 years were prescribed CBD according to the physician's judgement. Chart data were extracted from baseline (1 month before index date [CBD initiation]) until the end of the 12-month period, loss to follow-up, or CBD discontinuation, whichever occurred first.
Results: Chart data were available for 26 patients at baseline (LGS, n=17; DS, n=9; male, 73%); patient numbers refer to those with available data. Mean (range) age at seizure onset and index: 2.0 (0.1–10.0) and 11.8 (3.0–17.0) years, respectively. At baseline, 100% and 77% experienced motor and difficult-to-quantify seizures; 96% had cognitive impairment; 92%

were taking ≥1 antiseizure medication (14/26 [54%] clobazam). Median (Q1, Q3) CBD dose: 6.0 (4.5, 7.1) [n=12] and 7.3 (6.1, 8.1) [n=9] mg/kg/day at 6 and 12 months. Median percentage change from baseline (Q1, Q3) for motor seizures: −56.7% (−75.0%, −14.3%) and −60.0% (−86.7%, −33.3%) at 6 (n=20) and 12 months (n=15). Reduction in motor seizures of ≥50% and ≥75%: 13/20 (65%) and 5/20 (25%) at 6 months; 10/15 (67%) and 6/15 (40%) at 12 months. Mean (SD) motor seizure-free days/month: 1.5 (4.3), 2.4 (6.3), and 2.7 (5.5) at baseline (n=24) and 6 (n=18) and 12 months (n=15). At 12 months, retention on CBD for patients with follow-up data: 74% (14/19; 7 lost to follow-up). At 6 and 12 months, 14/20 (70%) and 8/15 (53%) experienced ≥1 adverse event of special interest.
Conclusion: Results support favourable CBD effectiveness and retention for up to 12 months in patients with LGS or DS in clinical practice.
Funding: Jazz Pharmaceuticals, Inc.

1499

Effect of the EpiTapp® method in combination with drug therapy on the quality of life of patients with drug-resistant structural focal epilepsy

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Purpose: *Background.* One of the main goals of rehabilitation programs is to improve the quality of life (QoL) of patients with various chronic diseases, including epilepsy. However, the issues of rehabilitation of adult patients with drug-resistant epilepsy remain not fully resolved.
Objective: to evaluate the impact of the author›s EpiTapp® method QoL of patients with pharmacoresistant structural focal epilepsy (SFE).
Method: *Material and methods.* The study involved 60 patients with drug-resistant SFE: main group – 30 patients (median age 33.5 years) with drug-resistant SFE, who in addition to their antiepileptic therapy upon the appearance of the first signs started an epileptic seizure regularly used the EpiTapp® method as an element of emergency self-help; control group – 30 patients (median age 39.5 years) with drug-resistant SFE who did not use the EpiTapp® wrist tapping method, but continued to receive previously selected antiepileptic therapy. QoL was assessed by the questionnaire method on the scale «Quality of life in epilepsy - QOLIE-31» translated by the authors.
Results: *Results.* When comparing QoL of two patient groups over a 6-month follow-up period, a statistically significant ($p<0.05$) positive dynamics in improving the indicators was demonstrated only in the main group; no dynamics was observed in the control group.
Conclusion: *Conclusion.* The author›s EpiTapp® technique improves QoL of patients with pharmacoresistant SFE and can be used as an additional method of rehabilitation.

1508

Anti-seizure medication and seizure cycle dynamics

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Purpose: Anti-seizure medication (ASM) is the main treatment for epilepsy, but finding an optimal regime can involve trial and error. Furthermore, methods to assess efficacy, to guide treatment decisions, are confounded by seizure cycles. We propose the possibility of incorporating seizure cycles into the assessment of ASM efficacy by using cycle information to provide weekly quantitative feedback. However, it is unclear if seizure cycles are stable over time or with ASM. The purpose of this study was to investigate seizure cycle stability with and without ASM changes.
Method: Three datasets of seizure times were investigated: 1. 1000 seven yearlong simulated seizure diaries and duplicate diaries with seizures removed; 2. electrocorticography detected seizures in a retrospective longitudinal cohort of people with medically refractory focal epilepsy on stable ASM (n=11); 3. November 2022 - February 2023 the Seer Medical app database was sampled for subjects with >12 weeks diary data, and ASM adherence data (n = 102). Seizure cycles changes were identified using an updating fixed-cycle phase-locking method. These changes were analysed according to the change in weekly seizure rate using the Kruskal-Wallis test with correction for multiple comparisons ($p<0.00005$).
Results: Seizure cycles change in phase, amplitude, and frequency over time. These changes occurred with and without ASM changes. Moreover, changes in ASMs did not always change seizure cycles, but only did so if the drug affected underlying seizure rate. More importantly, statistically significant negative correlations exist between seizure rate, the number of prominent seizure cycles, and also the phase-locking value (a measure of seizure cyclicity).
Conclusion: Seizure cycles are dynamic, exhibiting irregular and quasi-stationary patterns. Effective ASMs modulate seizure cycle amplitude, but the relationship between ASM efficacy, seizure likelihood, and time remains complex and poorly understood. Nonetheless, monitoring changes in seizure cycles offers valuable information about disease severity, providing early feedback for ASM treatment decisions.

1510

The efficacy and safety of fenfluramine in the treatment of Dravet syndrome and Lennox-Gastaut syndrome: evidence from randomized controlled trials

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Purpose: To evaluate the efficacy, safety, and tolerability of fenfluramine in drug-resistant epilepsy including Dravet syndrome and Lennox-Gastaut syndrome, and provide further evidence for the optimal dosage to guide clinical use.
Method: MEDLINE, Embase, Cochrane Library, and ClinicalTrial.gov were searched for relevant literature published from 1995 to November 1, 2022. Eventually, 3 randomized placebo-controlled trials on DRE (DS and LGS) with 469 patients were included.
Results: We pooled 469 patients from 3 RCTs. The primary outcome was at least 50% reduction in monthly seizure frequency (MSF) and the secondary endpoints were at least 75% reduction, near seizure freedom (seizure frequency ≤1), seizure freedom, as well as investigator- and caregiver/parents-rated clinical global impression improvement scale. It was found that fenfluramine (0.2 mg/kg/d, 0.4 mg/kg/d, 0.7 mg/kg/d) showed significant efficacy over placebo in terms of at least 50% reduction (*RR 2.67, 95%CI[1.59,4.48], P<0.001; RR 11.77, 95%CI[2.95,46.89], P<0.001; RR 3.26, 95%CI[1.96,5.42], P=0.002*, respectively) and at least 75% reduction (*RR 4.36, 95%CI[1.50,12.66], P=0.007; RR 15.35, 95%CI[2.12,111.18], P=0.007; RR 7.41, 95%CI[1.60,34.33], P=0.01,* respectively) in MSF from baseline. And significantly more patients receiving fenfluramine than placebo were rated as much improved or very much improved by both investigators (*RR 3.52, 95%CI[1.43, 8.64]*) and caregivers/parents (*RR 3.51, 95%CI[2.14, 5.75]*). The most common treatment-emergent adverse events were decreased appetite, diarrhea, fatigue, and weight loss, with no valvular heart disease (VHD) or pulmonary hypertension (PAH) observed in all participants.
Conclusion: Low-dose fenfluramine has shown good efficacy, safety, and tolerability in patients with DS and LGS, with no clinical evidence of VHD and PAH. Nevertheless, the long-term efficacy and safety of fenfluramine need to be verified in further studies.

1513

Two cases of severe skin reaction in patients with renal dysfunction caused by lacosamide

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Purpose: In clinical trials, lacosamide(LCM) has rarely been reported to cause skin rash, incidence being similar to that of placebo. These findings are consistent with real-world data; however, a few severe skin reactions have been reported. I report two patients with renal dysfunction who developed severe skin reactions with LCM.
Method: A 61-year-old female with a history of HTN, DM, and end-stage renal disease on hemodialysis, was admitted due to COVID-19. Acute pancytopenia was accompanied by subdural hemorrhage (SDH). Seizure was managed with levetiracetam. The patient recovered

and was discharged.
A month later, she presented with continuous focal motor seizures with awareness caused by non-adherence. Levetiracetam 1000mg/day and LCM 200mg/day were started. A week later she was seizure-free without any adverse events. Another week later, she visited emergency room due to weakness, tremor, rash, and pancytopenia. The antiseizure medication(ASM) s were stopped. Supportive care and immune modification therapy were provided. Unfortunately, she expired due to sepsis and toxic epidermal necrolysis.
Results: A 48-year-old male patient with IgA nephropathy developed left frontal lobe abscess. LCM, levetiracetam, and perampanel were administered to control seizure. The patient developed eosinophilia, rash, thrombocytopenia, and fever within a month, indicating drug reaction. ASMs were changed to valproate, topiramate, and clobazam. He recovered and was discharged.
Later he developed pneumonia, which required meropenem, which interferes valproate. Seizure recurred. Since the remaining ASMs were not suitable and assuming that LCM was not the cause among the previous ASMs, it was cautiously reintroduced. However, within a few days, eosinophilia, fever, and rash redeveloped. The rash improved with discontinuation.
Conclusion: While it may be coincidental, the use of LCM caused severe skin reaction in individuals with impaired renal function. The potential linkage between rash with LCM and renal dysfunction requires further investigation, but usage should be approached with greater caution.

1515

The role of the vascular factor in the formation of pharmacoresistance in epilepsy

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Purpose: To study the relationship between anatomical changes in cerebral and precerebral vessels, the state of cerebral hemodynamics and the development of pharmacoresistance.
Method: Research methods. Clinical, instrumental, statistical.
Results: The state of cerebral blood flow and venous hemodynamics was studied in 70 patients with drug-resistant epilepsy (Group 1), compared with the data of 30 patients with curable forms (Group 2). In group 1, there was a blood flow deficit in the anterior cerebral artery in 33.3%, in the middle cerebral artery (MCA) in 52.4%, in the posterior cerebral artery in 26.2%, in the basilar artery in 26.2% and for the vertebral (VA) - in 30.9%. In group 2, 25.0% had a deficiency of blood flow in the MCA, 32.1% in the PA. There were no signs of dilatation of the arteries in all examined patients (RI was within the normal range). Significantly more often signs of obstruction of venous outflow from the cranial cavity were revealed: 88.5% and 57.1%, respectively ($p<0.05$). Moreover, in group 1, obstruction of venous outflow from all parts of the skull with signs of intracranial hypertension (76.2%) was more often noted, only 5 respondents had obstruction of venous outflow from the anterior cranial fossa without signs

of increased intracranial pressure. Among patients of group 2, obstruction of venous outflow from the anterior cranial fossa (42.9%) was more often detected than from all parts of the skull (14.3%), signs of intracranial hypertension were observed in 32.1%.
Conclusion: Presence of cerebral hemodynamic disorders is associated with a resistant course of epilepsy.

1533
Real-world use of Cenobamate (CNB). A multicenter Italian experience

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Purpose: This study investigated early, real-world outcomes with CNB in a large series of drug resistant epilepsy (DRE) patients from Veneto region with a focus on outcome in patients with ≤5 previous anti-seizures medications (ASMs).
Method: Multicenter, retrospective, observational study. Demograpfhic, effectiveness and safety data sourced from clinical records of 16 hospitals.
Results: The study included 178 patients (127 and 74 with 3 and 6 months follow-up (FU) respectively). At baseline, median epilepsy duration was 24 years and median number of seizures in the previous 12 weeks was 24. The median number of prior and concomitant ASMs were 8 (2-18) and 3 (1-6), respectively. At 3 and 6 months mean CNB dosages were 166 and 205 mg; retention rates were 97,7% and 96%; the rate of seizure freedom (SF) was 17% and 15%; ≥75% responder rates (RR) were 31% and 39%, and ≥50% RR were 52% and 64% respectively. Seizures number significantly reduced from baseline (P<0,0001) at 3 (mean 31%, medi-

an 50%) and 6 months FU (mean 41%, median 62,50%). In 30 patients with ≤5 previous ASMs (median epilepsy duration 17,5 years), SF was 23% with 40% ≥75% RR and 56% of ≥50% RR. In 12/30 patients with 6 months FU, SF was 25% and ≥75% RR 82%. In the entire study population, at 3 and 6 months 45% and 25% reduced the number of concomitant ASMs, 53,5% and 30% reduced at least one ASM dose. The frequency of adverse events (AEs) and AEs leading to discontinuation were 30% and 1,5% at 3 months, 20% and 2,7% at 6 months. The most frequent AEs were drowsiness and dizziness.
Conclusion: CNB confirmed high effectiveness and retention rate in severe DRE, it allows to drugs load reduction. Our data showed a better response when CNB is used earlier. AEs were frequent but few led to discontinuation.

1536

Evidence for a between-sex anti-seizure medicine (ASM) efficacy difference: males respond better than females, as evidenced by valproate (VPA) suppression of EEG photoparoxysmal response (PPR)

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Purpose: Apart from pregnancy, between-sex differences have been identified in drug pharmacokinetics and drug-induced adverse effects. Yet, ASM *efficacy* differences among women versus men have not been described (Perucca, *Neurobiol Dis* 2014). Herein, we tested for sex differences in VPA's suppression of the PPR in naïve females versus males.
Method: We analyzed prospectively-acquired EEG data from sequential photosensitive ASM-naïve patients before and after VPA treatment. Patients were tested according to European guidelines (see ILAE website). The test-retest IPS procedure period was limited to 1.5 years, most however between 6-12 wks. Generalized PPRs were considered positive. Hz ranges were transformed into standardized photosensitivity range (SPR). An SPR value ≥3 was defined as VPA clinical response, a criteria used in Proof-of-Principle trials. Blood samples were collected to measure total plasma [VPA] concentration, shortly after several patient's EEG, when dictated by clinical need.
Results: A total of 48 patients (*27F, 21M; age range 8-50 yr*) met our criteria. Plasma [VPA] concentrations were known in 13 patients (average 67 mg/L, range=37-124). Males showed in all cases (21/21) a SPR decrement of at least 3, whereas females in 14/27 (51.85%) (p=0.0001) with PPR *elimination* in respectively 10/21(47.6%) versus 4/27 (14.8%). After VPA treatment, the median SPR decrement =7.0 in males and =3.0 in females. This difference in effect appears not to be VPA dose related, since the mean VPA dose was in males =847.6 vs. 736.7 mg/day for females. The median plasma total [VPA] concentrations obtained in a few patients was 51 mg/L in 5 male responders, 98 mg/L in 4 female responders and 99 mg/L in 4 female non-responders.

Conclusion: In 48 ASM-naïve patients with epilepsy plus photosensitivity, we found that all IPS-tested males suppressed SPR with VPA treatment compared to only half of the females. VPA doses nor [VPA] concentrations could explain this between-sex difference.

1553

Valproate vs lamotrigine, levetiracetam or topiramate for generalised epilepsies: supplementary analyses of the SANAD trials

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Purpose: There are increasing concerns about the teratogenic effects of valproate on the off-spring of men as well as women, as well as the possibility of transgenerational effects. We present additional subgroup analyses of the SANAD trials to identify patients most likely to benefit from valproate to inform treatment and regulatory decisions.
Method: SANAD I compared valproate, lamotrigine and topiramate (n=664) whilst SANAD II compared valproate with levetiracetam (n=520) as first-line treatments for generalised or unclassified epilepsy. Intention to treat (ITT) and per protocol (PP) analyses were undertaken for time to 12 month remission for subgroups: absence epilepsies, other generalised epilepsies, unclassified epilepsy. Regression models including interaction effects were fitted (Cox regression for ITT analyses, Fine & Gray regression for PP analyses). Estimates are Hazard Ratios (HR) with 95% CI.
Results: The overall ITT analyses (generalised or unclassified) indicate superiority of valproate over lamotrigine 1.32 (1.05 to 1.62).
ITT subgroup analyses indicate superiority of valproate over lamotrigine 1.44 (1.07 to 1.94) and levetiracetam 1.55 (1.14 to 2.11) for other generalised epilepsy.
The overall PP analyses indicate superiority of valproate over lamotrigine 1.37 (1.08 to 1.74), topiramate 1.37 (1.08 to 1.75) and levetiracetam 1.68 (1.30 to 2.15).
The PP subgroup analyses indicate superiority of valproate over lamotrigine 1.67 (1.19 to 2.34) and topiramate 1.42 (1.03 to 1.95) and levetiracetam 2.29 (1.59 to 3.30) for other generalised epilepsy, and valproate over lamotrigine 1.66 (0.98 to 2.82) and topiramate 1.89 (0.99, 3.58) for absence epilepsies.
Conclusion: The results confirm the superiority of valproate as a first line treatment for idiopathic generalised epilepsy. That superiority is greatest for our 'other generalised epilepsy' group – primarily those with tonic clonic seizures, who are at greatest risk or injury and other adverse outcomes. These results must be taken into account when making treatment and regulatory decisions.

1578

Perampanel in patients with refractory and super-refractory status epilepticus: add on therapy

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Purpose: To evaluate efficacy and safety of treatment with PER in patients with refractory and super-refractory SE in Intensive Care Unit
Method: We retrospectively analyzed treatment response, outcome, and adverse effects of all patients with refractory SE in Intensive Care Unit, Prasat Neurological Institute of Thailand who received add-on Perampanel between October 2021 to September 2022
Results: Twenty eight patients received perampanel, 14 males vs 14 female with mean age 50.68 [17-89] years, perampanel responders 12 (40.85%). Perampanel was the 4th -5th AEDs administration. In 18 patients (64.29%), a high-dose approach was used, with a median initial dose of 16 mg (range = 16-24). In six patients (50%), SE could be terminated after PER administration (median dose = 16 mg, range = 16-24 mg, all of them were in high-dose group). Clinical response was observed after a median of 16 hours (range = 8-48 hours), whereas electroencephalogram resolved after a median of 48 hours (range = 24-72 hours). Time to treatment response tended to be shorter in patients receiving high-dose PER (median clinical response = 16 hours vs 18 hours; electroencephalographic response = 24 hours vs 72 hours). No electrocardiogram abnormality found. Unfavorable in 10 patients (46 % high dose vs 54% standard dose), and good recovery was achieved in 18patients (58% high dose vs 42% standard dose). Total time of admission in ICU was shorter in responder group(14 vs 46 days).
Conclusion: Perampanel may be an effective add-on treatment for RSE and SRSE even in patients who failed multiple AEDs without major adverse effect and trended to reduce the time of admission in ICU.

1585

Safety, tolerability and pharmacokinetic findings from a first-in-human, randomized, double-blind, placebo-controlled trial of single and multiple ascending doses of PRAX-628 in healthy participants

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Purpose: Focal epilepsy is characterized by localized neuronal hyperexcitability, with current standard-of-care limited by tolerability issues and need for titration to avoid side effects, possibly due to inability to selectively target hyperexcitable states. PRAX-628 is a novel compound in development as a best-in-class treatment for adult focal epilepsy, with demonstrated superior selectivity for functional-state sodium channel hyperexcitability. Here we report preliminary first-in-human safety and tolerability related to predicted efficacy based on the mouse maximal electroshock seizure (MES) model.
Method: PRAX-628-101 was a randomized, double-blinded, placebo-controlled Phase 1 trial

investigating the safety, tolerability and pharmacokinetics of single (SAD) and multiple (MAD) ascending doses of PRAX-628 in healthy participants aged 18-55 years.
Participants were randomized 3:1 to receive either PRAX-628 or placebo in the fasted state, with SAD cohorts receiving single oral doses (5mg starting dose) and MAD cohorts receiving multiple doses (for 10 days). Safety and tolerability assessments included incidence and severity of adverse events (AEs), vital signs, 12-lead ECGs, physical examinations, clinical laboratory tests, and the Columbia-Suicide Severity Rating Scale (MAD only). Blood samples were collected for measurement of PRAX-628 plasma concentrations.
Results: A total of 40 participants completed the study (n=30 PRAX-628, n=10 placebo). PRAX-628 was well-tolerated at tested doses (5-45mg, SAD; 20 and 30mg, MAD). All AEs were mild, mostly transient and resolved without further intervention. No AEs led to study drug withdrawal. No SAEs, clinically significant findings on vital signs, ECG or neurological examination were observed. Pharmacokinetic data demonstrated dose-dependent exposure. PRAX-628 was well-tolerated at concentrations more than 15-fold the mouse MES EC_{50}, with a predicted therapeutic range at least 3-fold above cenobamate.
Conclusion: PRAX-628 demonstrated a favorable safety and tolerability profile in healthy volunteers. Building on preclinical work, these findings support once-daily dosing of PRAX-628 without titration to achieve therapeutically effective concentrations with potential for best-in-class efficacy.

1606

Long-term results with the novel anti-seizure medication, cenobamate, in a single center in Hungary

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Purpose: The aim of the present study was to retrospectively follow up the hospital records of patients taking cenobamate (CNB) in our centre. The study is an observational, descriptive study of clinical practice to assess the long-term efficacy and safety of CNB. Efficacy will be assessed in terms of the reduction in seizure rate and the dose of CNB used, and safety will be assessed by analysing the side effects observed during use.
Method: The data were collected from 61 patients enrolled in the YKP3089-C017 and YKP3089-C021 clinical trials who started taking CNB between 01.01.2013 and 31.12.2017 and continued taking CNB after the trials were completed. Additionally, 15 patients approved the pre-licensure named patient program (NPP) and started taking CNB until 30.09.2022 were also included. The follow-up periods was divided into 3 parts with 1, 6 and 10 years for patients enrolled in YKP3089-C017, 1 and 6 years for patients enrolled in YKP3089-C021 and 1 year follow-up for NPP.

Results: The first follow-up year the average seizure reduction was 51%, which increased to 57% at 6th year of follow-up and 61% of the 10th year. At 1 year 15% of the patients were seizure free. 29% of patients taking CNB could decrease the concomitant ASMs. Suspected adverse reactions causing CNB discontinuation were seizure status worsening, skin symptoms, headache, sleepiness, dizziness, eosinophilia, suicide thoughts, oncological problems and arbitrarily termination.
Conclusion: We found that CBM is a highly effective, well-tolerated ASM over long periods of time. Real world data is concordant with previous reports of efficacy in controlled studies.

1616
Observational clinical trial of cannabis in drug-resistant focal epilepsy adults

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Purpose:
To determine the effective dose, level of effectiveness and tolerability of purified cannabidiol as adjuvant treatment in focal drug resistant epilepsy adults.
Method: An open observational prospective study was performed. We included 55 patients with focal drug resistant epilepsy, with functional levels of writing and reading comprehension . All patients started cannabidiol treatment with a 100% CBD purified oil formula at 250 mg/day (mean: 4.1 mg/kg/day), titration progressively up to 20mg/kg/day according to clinical response and tolerability during 6 months. The criterion used to assess efficacy was the monthly percentage change in the number of seizures. Tolerability was evaluated through the adverse effects registry.
Results: 55 patients were included. Eleven patients did not complete the study, 9 dropped out and 2 patients were excluded due to protocol violation. The results analyzed are from the remaining 44 patients are: 87% of the patients (38) reduced 50% of their monthly seizures (5% (2) are seizure-free so far, and 32% (14) patients decreased more than 80% of their seizures), five patients (11%) presented a decrease of less than 50% of their usual seizure frequency, one patient presented an increase in his seizure frequency.
The average final dose was 335 mg/d (5 mg/kg/d), and 329 mg/d (4.7 mg/kg/d) in responding patients (≥50% seizure reduction). Fifteen patients (34%) did not report adverse events. The remaining 66% (29 patients) presented mild symptoms. Most of the patients presented only 1 type of adverse effect (41%), while the minority presented 2 (11%) and 3 types of adverse effects (14%). 60% of the patients who reported adverse effects were gastrointestinal, 16% drowsiness and 14% decreased appetite.
Conclusion: Adjuvant treatment with purified CBD in focal epilepsy is effective in 87% of cases and safe in all cases with 329 mg per day.

1629

Epilepsy treatment: experiences of people living with epilepsy (PLWE) on anti-epileptic drugs in Limpopo and Mpumalanga provinces, South Africa

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Purpose: This study aimed to determine and describe issues related to epileptic seizures and treatment-related effects among people living with epilepsy (PLWE) in rural communities in the Limpopo and Mpumalanga Provinces in South Africa.
Method: A quantitative cross-sectional survey was conducted among 162 PLWE using multistage sampling. Data were collected through a research assistant-administered questionnaire and analysed descriptively using SPSS.
Results: The study found that most PLWE experienced seizures sometimes (70.6% in Limpopo and 53.3% in Mpumalanga), and a considerable number always experienced seizures (20.6% in Limpopo and 40% in Mpumalanga). Many PLWE reported experiencing the side effects of anti-epileptic medications always or sometimes, which affected their ability to perform strenuous work and play with friends and caused fatigue. The treatment and epilepsy had adverse effects on the education and employment of PLWE, leading to school dropouts and job losses. PLWE also faced social and psychological challenges, including dependency, isolation, stigma, and discrimination.
Conclusion: The study highlights the need for improved access to information and awareness about epilepsy in rural settings. Government efforts should focus on improving care for epilepsy patients and reducing the adverse effects of treatment on their quality of life. Factors affecting healthcare use and treatment adherence, such as accessibility, availability, affordability, and individual beliefs, should be examined. There is a need for comprehensive support systems and interventions to address the social and psychological impact of epilepsy on PLWE.

1636

Real-world short term efficacy and safety of cenobamate (CNB) in patients with drug-resistant focal onset seizures: a single centre, retrospective, observational study

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Purpose: Drug-Resistant Epilepsy (DRE) is defined in ILAE as the failure of two Anti-seizure medications(ASMs) to achieve sustained seizure freedom. DRE leads to decreased quality of life, exposure to multiple ASM, and increase risk for SUDEP. CNB has dual anti-seizure activity resulting in the inhibition of voltage-gated sodium channels and is also a positive modulator of GABAA receptors. CNB is an adjunctive ASM in focal-onset seizures in adults with epilepsy with inadequate seizure control despite two ASMs. CNB is effective and well-tolerated in clinical trials. This study is an extension of the clinical trials, we assessed the real-world efficacy and safety of CNB in patients with DRE from the outpatient clinics in Royal Stoke University Hospital.
Method: This was a Single Centre, retrospective, Observational study. Data from clinical records of patients above 16 years were collected. Primary efficacy endpoint was seizure frequency reductions(≥90% ≥75%,≥50%,25%-50%,<25%). The frequency before starting CNB and at the last patient review was assessed. Adverse events(AEs)leading to discontinuation are used as a safety endpoint.
Results: The study evaluated 33 patients with a median follow-up of 151days of CNB treatment. Median epilepsy duration was 34years with a mean age of 44(age range 17-83).Prior to CNB, the median of seizures/month was 24.5.The mean daily dose of CNB is 139.The mean of prior discontinued anti-seizure medications(ASMs)and concomitant ASMs were 4.09 and 2.5. In the latest review, 30.3% had a seizure freedom rate of ≥90%.Seizure freedom of ≥75%-90%, ≥50%-75%; ≥25%-50%,<25%achieved by27.2%,15.1%,9%and18.1%respectively.CNB showed a retention rate of 90.9%.6 patients reported AEs with fatigue/somnolence being most common leading to 9% discontinuation. CNB significantly reduced the median number of seizures per month from 24.5 to 3.5.
Conclusion: More than 50% seizure freedom was achieved by72.7%of CNB treated patients. Concomitant ASMs usage was reduced in 61.76% of patients. In DRE, CNB was found to be effective and well-tolerated with good adherence.

Epidemiology

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Improving epilepsy care in Ontario, Canada: the impact of the provincial strategy for epilepsy care

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Purpose: In 2016, the Ontario Ministry of Health and Long-Term Care implemented the Provincial Strategy for Epilepsy Care to increase epilepsy surgery use. This consisted of an increase in the number of video-EEG beds and medical personnel, as well as the creation of District and Comprehensive Epilepsy Programs in the Province of Ontario. The objectives of this study were to assess whether the use of (1) epilepsy surgery, including (a) its receipt and (b) assessment for candidacy, and (2) other healthcare for epilepsy, including (a) neurological consultations, (b) emergency department visits, and (c) hospital admissions, changed since the Provincial Strategy was implemented.
Method: We used administrative health data and an interrupted time series design. Annual cohorts were created for July 1st to June 30th of each year between 2007 and 2019, comprising patients with drug-resistant epilepsy eligible for the Ontario Drug Benefit program with no history of cancer. We used segmented Poisson regression models to assess whether the annual incidence of each outcome changed between the period before the Provincial Strategy was initiated (July 2007 to June 2016) and the period after.
Results: The level and trend changes for the incidence of epilepsy surgery and assessment for candidacy were non-significant between the two periods. However, the lower 95% confidence limits for the level increases were close to the null value (epilepsy surgery: 48% [95% CI: 0%, 118%]; surgical candidacy: 41% [95% CI: -1%, 99%]). Statistically significant trend decreases were observed for neurological consultations (-10%, 95% CI: -15%, -5%) and hospital admissions (-7%, 95% CI: -12%, -1%).
Conclusion: These findings suggest that the Provincial Strategy increased the use of epilepsy surgery and assessments for candidacy. The program establishment was also associated with a declining incidence of neurological consultations and hospital admissions.

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Association of noise, air pollution, and heatwaves with epilepsy-related hospital admissions

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Purpose: The understanding of the association between seizures and environmental factors remains limited. This study aims to investigate the impact of chemical and acoustic pollution,

as well as meteorological variables, particularly heatwaves, on seizure-related hospital admissions.
Method: Data from 2,739 seizure-related hospital admissions in the Autonomous Region of Madrid, from January 2014 to December 2018, were analyzed. We examined the association between dependent variables including total seizure-related hospital daily admissions (TSHA), status epilepticus-related hospital daily admissions (SEHA), and epilepsy with recurrent seizures-related hospital daily admissions (ERHA), and independent variables such as daily mean concentrations of particulate matter (PM), PM subcategories PM10, PM2.5, NO_2, O_3, noise level, maximum and minimum temperatures, air pressure, sunlight hours, wind speed, relative humidity, and heatwaves (maximum daily temperature ≥35.6°C). Generalized linear models were employed to establish associations, accounting for seasonal trends and potential delayed effects using lag analysis.
Results: We found significant associations between TSHA and NO_2 levels at lag 1 (meaning one day after; RR 1.039; 95% CI 1.013-1.065) and diurnal noise levels at lag 2 (RR 1.015; 95% CI 0.988-1.042, non-statistically significant). ERHA exhibited associations with diurnal noise levels without lags (RR 1.020; 95% CI 1.000-1.041) and NO_2 levels at lag 1 (RR 1.051; 95% CI 1.018-1.085). World Health Organisation-recommended noise limits were exceeded on 99% days. Additionally, TSHA were associated with summer heatwaves at lag 7 (RR 1.098; 95% CI 0.996-1.212), although this result did not reach statistical significance. SEHA showed associations with diurnal noise levels at lag 11 (RR 1.040; 95% CI 1.002-1.078) and PM10 pollution levels at lag 12 (RR 1.083; 95% CI 1.002-1.165).
Conclusion: Pollution, particularly NO_2 and noise levels, as well as heatwaves, may increase the risk of epilepsy-related hospital admissions.

1535

Long-term epilepsy outcome in rural China: a 10-year longitudinal study

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Purpose: A large community-based epilepsy cohort in rural China, established in 2010, enabled the prospective assessment of the long-term mortality and seizure outcomes in the long term.
Method: Recruitment and baseline assessment was between January 2010 and December 2011. Assessments were conducted from March 2013 to October 2014, October 2015 to March 2016, and July 2020 to October 2021 to collect data on clinical characteristics, treatments, and survival status. For any participant who died during follow-up, detailed in-

formation on the date and cause of death was obtained using a specifically designed Verbal Autopsy Questionnaire. All cases were reviewed by a multidisciplinary expert panel and re-investigated if necessary.
Results: The cohort consisted of 610 people with epilepsy, among whom nearly 80% had seizures within one year. Almost a fifth were not taking ASMs at baseline indicating the treatment gap. During the follow-up, 52% had a remission of at least one year. At the last follow-up, 63.5% were not seizure-free, 8% were in terminal 5-year remission, and 13% died. The all-cause mortality was 13.91 (95%CI 10.89-17.53) per 1,000 person-years. Twenty-two people (33%) died suddenly and unexpectedly in a reasonable state of health in the week preceding death which was the leading cause of death in this cohort. The incidence of probable sudden unexpected death in epilepsy (SUDEP) was 3.48 (95%CI 2.09-5.46) per 1,000 person-years and the incidence of all suspected (probable and possible) SUDEP was 4.50 (95%CI 2.89-6.70) per 1,000 person-years during follow-up.
Conclusion: Despite over half of people having at least one-year remission during the follow-up, over 60% of them still had recurrent seizures at last follow-up. SUDEP was the leading condition responsible for fatalities in this cohort.

1554

Focal seizures indicative of diabetes prospective study on 26 cases at the specialty hospital center of Nouakchott Yahya Bouke Specialty hospital center - Nouakchott Mauritania

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Purpose: The etiologies of focal seizures are numerous, including metabolic diseases such as diabetes. These seizures are more common during hyperglycemia without ketosis; however, they are less frequently mentioned as a way to identify diabetes.
Method: During the 96-month period from February 1, 2019, to March 1, 2023, we conducted a descriptive prospective study on the recruitment of patients hospitalized in the neurology department of the specialty hospital of Nouakchott for focal seizures connected to the initial detection of diabetes. We did not include known diabetic individuals, epileptic seizures with symptoms, or known epileptic patients.
Results: There are 26 patients, with an average age of 52 years and a little female predominance (a sex ratio of 1.36). The focal seizures were primarily motor in nature and occurred in isolated areas (tables 1 and 2). The average blood sugar level was 3.65 g/l, associated with glucosuria but without ketonuria, and the average level of glycated hemoglobin (HBA1C) was 9.4% (Figure 1). In 24 patients, natremia and osmolality were both normal. 14 patients had interictal electroencephalograms (EEGs), and they were all normal.
Cerebral imaging was normal (mostly performed by a cerebral scanner for 12 participants and a cerebral MRI for 2 cases). In the acute period, all patients are treated with insulin therapy, rehydration, and anticonvulsant medication. The evolution was positive and noticeable in 18

patients (69.2%) within the first 48 hours and late beyond 72 hours in 7 patients (26.9%). One patient died as a result of a seizure.
Conclusion: The search for diabetes must be systematic in the face of initial focal seizures, allowing for rapid, effective, and tailored etiological treatment. Unfortunately, diabetes continues to be a major public health issue, particularly in underdeveloped nations.

1565

Prevalence of seizures in thalamic brain tumors: a single centre experience and a meta-analysis

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Purpose: Current literature shows that the thalamus plays an indirect (secondary) role in epileptogenesis. However, till date, the question of the thalamus being a primary seizure generator remains unanswered. In our study, we aimed to demonstrate the presence of seizures in those with thalamic tumor alone, which suggest that the thalamus could be a primary seizure generator. This study studied the prevalence of seizures in patients with thalamic tumors in our center and via a meta-analysis.
Method: This study included a cross-sectional study and a meta-analysis. Medical records of patients diagnosed with gliomas between January 2008 and December 2020 were reviewed. In the meta-analysis, 22 studies relevant to the subject matter were identified from several bibliographic databases up to July 31, 2022. The PRISMA guidelines for conducting meta-analysis were followed.
Results: Out of the 239 glioma patients, fourteen had thalamic tumors of which four presented with preoperative seizures (28.6%). In the meta-analysis, the pooled prevalence of seizures in thalamic tumors was 17.0% (95% CI, 14 to 21%; range, 5.3%-35.0%). The prevalence of seizures in those without cortical involvement was 14.3% in our cohort, and the pooled seizure prevalence was 17% (95% CI, 12-23%; range, 7.1-22.4%) in the meta-analysis regardless of the tumor types.
Conclusion: In patients with thalamic tumors, even without cortical involvement, seizure occurrence is not uncommon (17%), suggesting that thalamus could be the primary seizure generator.

1568

Meningioma oedema and seizures – a systematic review and meta-analysis

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Purpose: Meningiomas are primary intracranial neoplasms that are commonly associated with oedema. Seizures are often a presenting feature and can even remain or occur de novo in the early (within one week) or late (after one week) periods following treatment. A systematic review and meta-analysis in 2016 by Englot et al found that oedema increased the risk of preoperative seizures but only eight studies were included. Furthermore, an analysis of postoperative seizures was not possible. Our aim is to perform an updated review to guide prognostic modelling across the treatment pathway.
Method: A comprehensive and systematic literature search identified 2,238 unique papers resulting in 42 unique studies that provided either contingency tables or unadjusted effect sizes comparing seizure status in patients with and without oedema.
Results: When pooling effect sizes, we found that preoperative oedema increased the odds of preoperative seizures; odds ratio (OR) 3.52; 95% confidence interval (CI) 2.52 to 4.91; 28 studies (k); 7337 participants (n); moderate heterogeneity (I^2) 62%. We also found that preoperative oedema increased the odds of both early (within one week) postoperative seizures; OR 1.50; 95% CI 1.00 to 2.25; k =7; n = 2,801; low I^2 0%, and late (greater than one week) postoperative seizures; OR 1.97; 95% CI 1.72 to 2.26; k = 14; n = 4,314; low I^2 0%. Two studies looked at oedema and seizures following stereotactic radiosurgery, oedema was associated with increased odds of seizures in both; OR 3.75 CI 0.68 to 20.58, and OR 47.68 CI 6.03 to 377.21.
Conclusion: We have redemonstrated that preoperative oedema increases odds of preoperative seizure. For the first time in a meta-analysis, we have demonstrated that preoperative oedema also increases the odds of postoperative seizures in early and late postoperative periods, albeit to a lesser extent.

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Loss of consciousness in youth: does it differ among distinctive fields students?

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Purpose: To assess the frequency, differences, and associated factors of loss of consciousness (LOC) among students at three different faculties of Vilnius University
Method: An electronic questionnaire was filled in via the internal mail of Vilnius University. The questionnaire consisted of 33 questions to assess the type of loss of consciousness expe-

rienced and 14 questions to assess the HADS scale. Students from the faculties of Philology, Law, and Medicine were interviewed. Statistical analysis was performed using IMB SPSS Statistics V.28.0. Quantitative data are presented in frequencies and mean (SD) and qualitative data are compared using the chi-square test of independence ($p<0.05$).
Results: In total, 308 students took part in the analysis: philologists (n=132), 102 medical and 74 law students. The mean age was 21±3 years, and 90.6% were female. More than half (58.4%) reported having experienced at least one episode of unconsciousness: 60.8% of medical, 59.8% of philology, and 54% of law students. The mean age at first loss of consciousness was 14.4±4.3 years with the most frequent provoking factor as emotional stress (45.1%). General weakness (65.9%), dizziness (58.1%), visual changes (53.3%), tinnitus (45.5%), and pallor (37.3%) were the most frequent symptoms before the loss of consciousness and were more frequently reported by medical students (94.1%) (law - 83.8%, philology - 78%, $p=0.003$. Pre-syncopes were also statistically significantly related to the number of hours per week spent studying students studying 12 or more hours per week were more likely to experience this disorder ($p=0.04$). Students with co-morbidities were more likely to experience syncope ($p<0.001$).
Conclusion: Loss of consciousness does not differ significantly between Philology, Law, and Medicine students, but medical students are more likely to experience pre-syncope, which is triggered by emotional stress and long study hours.

1602

The Norwegian pediatric epilepsy cohort study – population-based occurrence of seizures, syndromes and etiologies

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Purpose: The Norwegian Pediatric Epilepsy Cohort Study, NorPEC, provides population-based information on occurrence of epilepsy in children and adolescents and distribution of seizure types, etiologies and epilepsy syndromes according to the most recent ILAE classifications.
Method: The study platform is the Norwegian Mother, Father and Child Cohort Study (MoBa), a nationwide, population-based cohort study prospectively following children with questionnaires and linkages to nationwide health registries since pregnancy. Within MoBa, NorPEC is a nested case-cohort study. After medical record review, all epilepsy diagnoses have been validated and seizures, syndromes and etiologies classified by two experienced consultants according to ILAE clinical definitions and classifications.
Results: The NorPEC study identified 1336 potential epilepsy cases among the 113,132 MoBa participants. MoBa participants diagnosed with epilepsy until 2012 are described previously by the Epilepsy in Young Children Study.
The current data collection includes adolescents in MoBa receiving epilepsy diagnoses 2013

through 2020. Among 714 new potential epilepsy cases, data collection is completed in 434 (60.8%), from which 300 (69.1%) have verified epilepsy. Median age at data collection was 16.3 years and at onset 10.3 years. Seizure onset was focal in 60.3%, generalized in 38.3% and unknown in 6.7%. 1.3% had both focal and generalized onset seizures.
Cause of epilepsy was identified in 20.5% (15,3% structural, 4,0% definite genetic, 1,0% metabolic, immunologic or infectious). 33.0% had presumed genetic etiology and 46.7% unknown etiology.
We identified an ILAE epilepsy syndrome in 154 (51.3%), most prevalent idiopathic generalized epilepsies in 78 (26%) (including 32 CAE, 19 JAE, 13 JME and 14 GTCA). Self-limited focal epilepsies of childhood occurred in 55 (18.3%). Only 7 of 35 encephalopathic patients had a defined ILAE syndrome.
Conclusion: This new cohort of adolescents provides population-based occurrence of epileptic seizures, syndromes and etiologies according to the new ILAE classifications.

Funding: Foundation Dam and South-Eastern Norway Regional Health Authority.

1642

Patterns of antiseizure medications prescriptions among pregnant people with epilepsy: a utilization study in four Canadian provinces

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Purpose: This study aimed to examine the trends of ASMs utilization among pregnant people in Canada.
Method: This population-based utilization study used data from Canadian Mother-Child Cohort (Manitoba [MB], Saskatchewan [SK], Alberta [AB] and Quebec [QC]) between 1998 and 2019. We focused on ASMs used throughout the pregnancy and different generations of ASMs. We used calculated the utilization patterns of different ASMs used. A subgroup analysis of socioeconomic status (SES) was conducted.
Results: We included 274,182, 245,899, 533,402 and 236,757 people from MB, SK, AB and QC respectively. Epilepsy prevalence was 0.6% (1,759 cases) in MB, 0.7% (1,774 cases) in SK, 1% (5,048 cases) in AB and 0.55% (1232 cases) in QC. ASMs were used among 3,726 (1.4%), 1674 (0.6%), 12,830 (2.4%) and 6,325 (2.7%) pregnancies in MB, SK, AB and QC, respectively. The combination of first-first generation ASMs decreased from 97.7% to 44.2% in MB, 90.3% to 17.6% in SK 58.73% to 39.11% in AB and 69.2% to 0% in QC. The first-second generation combination increased from 0% to 10% in MB, 0% to 9.2% in SK, 6.03% to 8.06% in AB and 30.8% to 66.7% in QC, while the second-second generation combination increased from 0% to 45.8 % in MB, 9.7% to 73.2 % in SK, 35.2% to 52.8% in AB and 0% to 25.0% for QC. The prevalence

of utilization was 31.5%, 27.6%, 12.6% and 42.7% among low SES in MB, SK, AB, QC respectively. In the group of pregnant people without epilepsy, gabapentin and clonazepam were the most commonly used ASM in MB and AB, while lamotrigine and gabapentin were the most commonly used in SK and clonazepam, Pregabalin and valproic acid were the most commonly used in QC.
Conclusion: The findings highlight variations in ASM prescribing practices, adoption of new-generation ASMs, and the influence of socioeconomic factors on utilization.

Epilepsy and Reproductive Health

1447

Reproductive patterns in individuals with epilepsy; a nationwide cohort study

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Purpose: We studied sex-specific reproductive patterns in individuals with epilepsy.
Method: We carried out a prospective population-based register study of all individuals of reproductive age (15-45 years) living in Denmark between January 1st 1982 and December 31st 2018. Study participants with epilepsy were identified using diagnostic information (ICD-8: 345 excluding 345.29 and ICD-10: G40) from the Danish National Patient Register. Births were identified from the Danish Medical Birth Register. Cohort members were followed from 15 years of age until childbirth, 45 years of age, emigration, death, or end of follow-up (December 31st, 2018), whichever came first. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazard models.
Results: We included a total of 2,396,180 individuals (1,227,240 males and 1,168,940 females) of reproductive age, including 48,420 with epilepsy before or during follow-up (24,960 males and 23,460 females) with a mean (SD) age at diagnosis of 15,7 (11,4) years. Males with epilepsy had a lower incidence rate (IR) of births (IR = 223, 95% CI; 217, 229) per 10,000 person years compared to males without epilepsy (IR = 304, 95% CI; 303, 305). Similarly, females

with epilepsy had a lower IR of births (IR = 380, 95%CI 372, 389) per 10,000 person years compared to females without epilepsy (IR = 428, 95%CI 426, 429). Compared with the general population, the HR of having children was lower in males with epilepsy (HR 0.59, 95%CI 0.57, 0.60) than in females with epilepsy (HR 0.73, 95%CI 0.71, 0.75), p-value<0.0001.
Conclusion: We found that individuals with epilepsy of reproductive age are less likely to become parents than individuals in the general population, and that this tendency is more pronounced in males than females with epilepsy. The contrast observed may be due to sex-specific differences in biological and/or social effects of epilepsy on reproduction.

1457

The placental kinetics of cannabidiol: an *ex vivo* perfusion study

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Purpose: In the absence of safety data in humans, the use of cannabidiol (CBD) is not recommended during pregnancy. Yet >50% of pregnancies in women with epilepsy are unintended, making fetal exposure to CBD possible. As a small-molecule, highly lipid-soluble drug, CBD is likely to distribute into the placenta and cross it. To estimate the placental distribution profile of CBD and its potential short-term placental effects, we conducted an ex-vivo perfusion study in human placentas.
Method: Placentas were obtained from cesarean deliveries of healthy women. Selected cotyledons were cannulated and perfused for 180 min with medium containing CBD at 250 ng/mL (0.796 µM; low therapeutic concentration) (n=8) or 1000 ng/mL (3.18 µM; high therapeutic concentration) (n=8). Cotyledons perfused with the vehicle served as control for gene expression analysis. CBD concentrations were determined at 180 min in the medium and placentas of the 250 ng/mL group using LC-MS/MS analysis. A customized gene panel array was used to analyze the expression of carrier genes in the perfused placental cotyledons.
Results: CBD concentrations at the fetal compartment were one-fifth of those measured in the maternal compartment (median 59 ng/mL; range 48-72 ng/mL, vs. 280 ng/mL, range 159-388 ng/mL, respectively; p<0.01). CBD accumulated in the placental tissue with a high variation across samples (median 5342 ng/g tissue; range 1066-9351 ng/g tissue). Perfusion with 1000 ng/mL CBD but not with 250 ng/mL CBD was associated with down-regulation of the folate 1 and transcobalamin receptors in placental tissue (61.6 and 63.1 % of controls, respectively, P<0.05).
Conclusion: The placenta acts as a depot compartment for CBD, slowing-down its distribution to the fetus. This phenomenon might yield flatter but prolonged fetal CBD levels *in vivo*. The clinical significance of CBD sequestration in the placenta has yet to be clarified.
This study was supported by the ISF grant #2054/18.

1460

Antiseizure medication use during pregnancy and attention deficit hyperactivity disorder: a population-based cohort study

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Purpose: We aim to study whether the association between ASMs treatment during pregnancy and attention deficit hyperactivity disorder (ADHD) differs among infants of all pregnant people, pregnant people with epilepsy (PPWE), and pregnant people without epilepsy (PPWOE).
Method: We conducted a population-based retrospective cohort study of pregnant people in Manitoba, Canada, from 1998 to 2021. We examined the association between ASMs exposure during 2nd and 3rd trimesters and the risk of ADHD in infants of all pregnant people, PPWE and PPWOE. We conducted Cox proportional hazards regression models and adjusted for maternal age, pain diagnoses, psychiatric disorders, diabetes, hypertension, urban/rural, socioeconomic status, multiple births and teratogenic drugs exposure in 1st trimester.
Results: We included 297,734 pregnant people in our cohort, including 4,187 ASM-exposed pregnant people, 881 PPWE, and 3,306 PPWOE. In infants of pregnant people exposed to ASMs inutero, we observed a significant increase in the risk of ADHD with an adjusted hazards ratio (aHR) of 1.28, 95%CI (1.08-1.52) compared with infants of unexposed pregnant people. We found a non-significant increased ADHD risk (aHR 0.77, 95%CI (0.53-1.11)) among infants of ASM-exposed PPWE when compared with unexposed PPWE. In infants of ASMs exposed PPWOE, we observed a significant increased risk of ADHD (aHR 1.40, 95%CI (1.13-1.73)) when compared with infants of unexposed PPWOE.
Conclusion: ASM exposure in pregnant people was associated with a significant increase in ADHD risk. ASMs for non-epilepsy indications must be rationalized, especially when alternate treatments are safer for pregnant people. Larger studies among PPWE are recommended to better identify and separate the effect of ASMs from underlying epilepsy.

1482

Women with epilepsy across the lifespan

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Purpose: To evaluate if women with epilepsy (WWE) receive the care recommended in Provincial guidelines and by epilepsy experts for gender-specific and sex-specific health issues, including fertility, family planning, contraception, teratogenicity, management during and after pregnancy, safety while caring for children, hormonal influences on seizure frequency, and bone health.
Method: A Canadian cross-sectional anonymous survey open to patients seen in the Epilepsy Clinic or admitted to the Epilepsy Monitoring Unit at London Health Sciences Centre, with a history of epilepsy, and who identify as a woman or who were assigned the female sex at birth was launched in December 2022. Participants were 18 years old or older.
Results: Preliminary results of 80 participants, mean age of 37.2 (range 18-66). Of the WWE who reported menses affecting their seizure frequency, 81% (n=21) discussed this with their physician, with no treatment changes for 70.6% (n=17). Only 37.7% (n=69) used contraception, of which 38.5% used IUDs and 23.1% used hormonal contraceptives (n=26). 63.2% (n=68) were advised to take folic acid, of which, the most common doses were 1 mg used by 25.6% and 5 mg used by 25.6% (n=43). 50% (n=38) of pregnancies were unplanned. 39.5% (n=38) of WWE who had been pregnant had a mental health diagnosis before pregnancy and 30.6% (n=36) were screened for postpartum mood disorders. Only 47.1% breastfed their children and 35.3% discussed the safety of using antiseizure medications while breastfeeding with a physician (n=34). 88.5% (n=61) of participants were not diagnosed with a bone condition. 61.7% were advised to take vitamin D, 28.3% were advised to take calcium supplements, and 35% received no bone health counselling (n=60).
Conclusion: Most WWE receive recommended counselling for some issues, e.g., bone health, but not for other issues, e.g., screening for postpartum mood disorders. Continued research and training are needed to improve the care WWE receive.

1603

Risk of major congenital malformations with exposure to antiseizure medications: an update from the EURAP registry

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Purpose: In this first update since 2018, EURAP provides information on the occurrence of

major congenital malformations (MCMs) with exposure to the most frequently used antiseizure medications (ASMs).
Method: This prospective cohort study is based on the EURAP registry, including data from ASM-exposed pregnancies. Follow-up data were obtained up to 1 year after birth. The primary objective was to compare the risk of MCMs in offspring exposed prenatally to monotherapy with one of eight commonly used ASMs. Logistic regression was used for comparisons between treatments, adjusting for potential confounders and prognostic factors. We also analyzed time trends in the prevalence of MCMs across 4 time periods: 1998-2004, 2005-2009, 2010-2014, and 2015-2022.
Results: 9840 pregnancies were exposed to one of the eight ASMs (2485 more than the last analysis). MCMs were recorded in 153/1549 (9.9%) pregnancies for valproate, 9/142 (6.3%) for phenytoin, 21/338 (6.2%) for phenobarbital, 121/2255 (5.4%) for carbamazepine, 10/204 (4.9%) for topiramate, 110/3584 (3.1%) for lamotrigine, 13/443 (2.9%) for oxcarbazepine, and 33/1325 (2.5%) for levetiracetam. MCM prevalence was related to ASM dose at the time of conception for valproate, phenobarbital, and carbamazepine. The overall MCM prevalence decreased progressively over time from 6.1% in 1998-2004 to 3.7% in 2015-2022, in parallel with a reduction in pregnancies exposed to valproate or carbamazepine and an increase in those exposed to levetiracetam or lamotrigine. This decrease in MCM prevalence was significant on univariable analysis [odds ratio: 0.59 (95% CI, 0.45-0.79)], but not after adjustment for changes in ASM prescription patterns over time.
Conclusion: With this expanded database, the lowest prevalences of MCMs were seen with exposure to levetiracetam, lamotrigine, and oxcarbazepine. Over time, the overall MCM prevalence declined markedly in parallel with a shift in ASM use, with a drop in exposures to valproate and carbamazepine in favor of levetiracetam and lamotrigine.

1628

The love hormone and seizure control: a review of oxytocin's impact on epilepsy management

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Purpose: The purpose of this paper was to review the current state of knowledge on the potential use of oxytocin as a therapy for epilepsy, including its mechanisms of action and clinical implications.
Method: The paper provides a comprehensive review of preclinical and clinical studies investigating the effects of oxytocin on seizure activity and outcomes in epilepsy. The literature search was conducted using relevant databases and included studies published up to the present time.
Results: Preclinical studies have demonstrated that oxytocin has antiepileptic effects, reduc-

ing seizure activity and improving seizure outcomes in animal models of epilepsy. Clinical studies have suggested that oxytocin may reduce seizure frequency and severity in some epilepsy patients. However, the evidence is limited, and further research is needed to establish the efficacy and safety of oxytocin as a therapeutic option for epilepsy.
Conclusion: Oxytocin shows promise as a novel therapy for epilepsy management based on preclinical and limited clinical evidence. However, additional well-designed clinical trials are necessary to confirm its efficacy and safety and to determine the optimal dosing and administration protocols. Oxytocin research also has broader implications for understanding social behavior and neurological disorders.

1641

In-utero use of gabapentin during pregnancy and the risk of attention deficit hyperactivity disorder: a population-based cohort study

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Purpose: Gabapentin is a new-generation antiseizure medication approved for epilepsy. Due to the perceived safety in pregnancy and efficacy in reducing pain, there has been an increase in the off-label use of gabapentin. We aimed to study the association between gabapentin treatment during pregnancy and the risk of attention deficit hyperactivity disorder (ADHD) risk among all pregnant people.
Method: We conducted a population-based cohort study among pregnant people in Manitoba, Canada from 1998 to 2021. We examined the association between gabapentin exposure in-utero during 2nd and 3rd trimesters and the risk of ADHD in infants. Cox proportional hazards regression models were used, adjusted for maternal age, pain diagnoses, psychiatric disorders, diabetes, hypertension, area of residence, socioeconomic status, multiple births and teratogenic drugs exposure in the 1st trimester.
Results: A total of 1057 pregnant people were exposed to gabapentin during their 2nd or 3rd trimesters of pregnancy. We found a significant increased risk of ADHD in children, with an adjusted hazard ratio (aHR) of 1.82, 95%CI (1.10-3.02), when compared with infants of unexposed pregnant people.
Conclusion: Gabapentin exposure in pregnant people was associated with a significant increased risk of ADHD in infants. Clinicians should be aware of the benefits and potential risks of prescribing gabapentin during pregnancy.

Epilepsy in Older People

1532

Prognostic factors of unprovoked seizures in patients with Alzheimer's disease

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Purpose: Evaluate the incidence rate and clinical prognostic factors for unprovoked seizures in patients with Alzheimer's disease (AD)
Method: This is a retrospective observational cohort study conducting at Maharaj Nakorn Chiang Mai hospital. Demographic, clinical, and dementia-related characteristics including medical treatment for dementia, use of antidepressants or antipsychotics, neuroimaging, and electroencephalographic finding were collected. Incidence and hazard ratios for unprovoked seizure within 10-year follow-up time were estimated. Survival analysis was performed by fitting univariable and multivariable Fine-Gray competing-risks regression with death as competing risk. Multivariable regressions were performed on variables studied in previous studies or significance or that were strong in the univariable analysis. Time was calculated from the AD diagnosis to the first unprovoked seizure or censoring at death or end of study, whichever came first. Complete case analysis was used for primary analysis.
Results: Of the 502 AD patients, 64.7% were female. Their mean age was 76.6 years and 82.1% had mild to moderate dementia. During the 10-year follow-up period (median follow-up time 4.1 years; IQR, 1.4-6.8), 41/502 AD patients (8.2%) developed unprovoked seizures. The median time from the diagnosis of AD to the occurrence of first unprovoked seizure is 3.1 years (IQR, 0.8-5.1). The incidence rate was 18.84 per 1000 person-years. Twenty (48.8%) had recurrent seizures. In multivariable Fine-Gray competing-risks regression modeling, significant independent prognostic factors of first unprovoked seizure were severe dementia (CDR-3) (HR, 6.77; 95% CI, 1.11-41.26), antidepressant use (HR, 2.69; 95% CI, 1.27-5.71), cortical lesion(s) (HR, 2.79; 95% CI, 1.23-6.33), and severe white matter lesion(s) (HR, 4.00; 95% CI, 1.21-13.22).
Conclusion: Epileptic seizures were not uncommon in AD and could occur in any point during the course of dementia. Greater degree of dementia severity, antidepressant use, cortical lesion and high vascular burden were independent prognostic factors for unprovoked seizures in patients with AD.

1630

New anti-amyloid therapies make screening for seizures critical for patients with Alzheimer's disease

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Purpose: Monoclonal antibody (anti-amyloid) treatments have recently been approved in the US and are being considered for approval in the EU, Japan and China for the treatment of Alzheimer's disease (AD). Seizures are an absolute contraindication to treatment with these agents due to risk for status epilepticus in those developing cerebral microhemorrhage or edema. As a field we are only beginning to understand the prevalence of seizures in individuals with AD. The literature indicates that the rates of seizures in AD are much higher than initially recognized and range from 10% to 64% (Vossel et al. 2017). This case report demonstrates the importance of systematically screening for seizures in individuals with AD when considering treatment with a monoclonal antibody.
Method: Patients presenting to a university-based geriatric memory clinic were screened for seizures using a modified version of the seizure screen questionnaire developed by Baker et al. (2019). The patient reported herein had a positive seizure screen followed by a targeted interview and referral for a High Density (HD)-EEG. The patient's diagnosis of AD was supported by a positive FDG-PET scan with a pattern of hypometabolism consistent with AD.
Results: The patient's spouse reported staring episodes not previously evaluated as possible seizure activity. The HD-EEG evaluation indicated abnormal findings due to the presence of left temporal discharges; electronic source localization was performed on the main focus which was estimated to be in the left medial temporal region. The patient was placed on levetiracetam and has remained seizure free for the past four months. Planned treatment with monoclonal antibody was aborted.
Conclusion: Status epilepticus has been reported with monoclonal antibody treatments for AD. Patients with AD are not routinely screened for possible seizure activity. Standard seizure screening protocols are essential when considering monoclonal antibody treatments for AD.

Epilepsy in Resource-restricted Settings

1472

Comparison of the quality of life (QOL) of people with epilepsy receiving home-based and clinic-based epilepsy care using the European quality of life five-dimension three-level (EQ-5D-3L) scale

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Purpose: To compare the QOL between people with epilepsy receiving home-based care (HBC) and routine clinic-based care (CBC).
Method: The people with epilepsy enrolled in this study were already part of a community-based randomized controlled trial conducted to compare two different types of epilepsy care on antiepileptic adherence among people with epilepsy (Singh G et al. Epilepsia Open. 4(2):264-274). The present study is a cohort study where the two cohorts, one receiving home-based epilepsy care (n = 97) and the other receiving routine clinic-based epilepsy care (n = 76), were compared for QOL at two points in time, i.e., baseline (at enrolment) and after 24 months of receiving epilepsy care, using the European Quality of Life Five-Dimension Three-Level (EQ-5D-3L) scale.
Results: The mean EQ-5D-3L index scores for the HBC group at baseline were 0.88 ± 0.15, and after 24 months, the scores increased to 0.94 ± 0.17. The baseline mean index scores for the CBC group were 0.89 ± 0.21, and after 24 months, the value increased to 0.90 ± 0.19. The mean difference in QOL in the HBC group showed a higher difference than in the CBC group (0.06 ± 0.1 versus 0.01 ± 0.1), but the difference was found to be statistically not significant at p = 0.067. As per the five dimensions of the EQ-5D-3L scale, i.e., mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression, there was a decrease in the number of PWE reporting problems among both groups after 24 months of epilepsy care.
Conclusion: The results showed a higher QOL among the people in the HBC group as compared to the CBC group, but the difference was not statistically significant. There was an improvement in QOL from baseline after dedicated care in both groups. The problems related to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression have been significantly reduced in the HBC group.

1519

The impact of a newly established specialized pediatric epilepsy center in Tanzania: an observational study

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Purpose: This study aimed at evaluating the impact of a newly established clinic for the diagnosis of epilepsy in pediatric age in a resource-limited center (Ifakara, Tanzania).
Method: Patients aged 0-18 years referring to the Paediatric Epilepsy Unit of Saint Francis Referral Hospital were recruited. Demographic and clinical data were collected through Kobo Toolbox (https://www.kobotoolbox.org/). A descriptive analysis of the data was conducted.

Results: 143 patients were evaluated and for 48 of them an EEG was recorded (EEG abnormalities detected in 80,85% of the cases). The diagnosis of epilepsy was confirmed in 87 patients. Focal epilepsy was diagnosed in 57 patients, generalized epilepsy in 24 patients and forms of unknown onset in 6 patients. Epilepsy was excluded for 9 children. Etiologies included hypoxic-ischemic encephalopathy (39%), Central Nervous System infections (3.4%) and genetic diseases (3.4%). A specific epilepsy syndrome was diagnosed for 16 patients. 74 patients were already under treatment and the most used antiseizure medication was phenobarbital (43.36%), followed by carbamazepine (16.08%), sodium valproate (11.19%), phenytoin (2.8%) and lamotrigine (0.7%). Therapeutic changes were proposed to 95 patients, more frequently consisting of withdrawing phenobarbital (39.16%) and switching to sodium valproate (27.97%), switching to or adjusting carbamazepine dosage (27.27%), starting prednisone (2.8%). 73.33% of the patients achieved a complete seizure freedom at the fourth follow-up.
Conclusion: Our study highlights that the organization of well-structured pediatric epilepsy centers may substantially improve diagnostic and therapeutic management in resource-limited countries. For the first time in a resource-limited country, a clinical characterization of the epilepsy types according to the latest international guidelines was made, leading to targeted treatment. The study suggests two specific aims for resource limited countries-tailored global actions:
· the cut of the costs to ensure the availability of effective broad-spectrum drugs (like Valproate);
· the promotion of education programmes on diagnostic and therapeutic management of epilepsy in pediatric ages.

1562

How to successfully establish an epilepsy care center in resource-limited countries

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Purpose: The aim of the current study was to systematically review the literature on establishing epilepsy care centers in resource-limited nations in the world and to provide a comprehensive roadmap on this significantly needed endeavor. This work may provide guidance on how to develop an epilepsy care center in other resource-limited places in the world.
Method: Web of science, Science Direct, and MEDLINE (accessed from PubMed) from inception to March 2023 were systematically searched for relevant published manuscripts. In all electronic databases, the following search strategy was implemented and these key words were used (title/abstract): epilepsy AND resource. The inclusion criteria were all original studies and articles written in English.
Results: We could identify nine manuscripts on how to successfully establish an epilepsy care center in resource-limited countries. Two models were identified for such an endeavor: developing a team of trained healthcare professionals (e.g., in Iran, India, China, Vietnam) or a

twin affiliation between an advanced epilepsy surgery program in a developed country and a starting program in a developing country (e.g., in Georgia, Tunisia).
Conclusion: In order to successfully establish an epilepsy care center in resource-limited countries four pillars are needed: presence of skilful healthcare professionals, having access to basic investigative technologies (i.e., MRI and EEG), a careful planning, and raising awareness.

1572
Semiology of seizures in patients with temporal epilepsy

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Purpose: The semiology analysis of seizures in epileptic patients is necessary for a better understanding. The study aims to examine semiology seizure, and characteristics of disease in a group of patients with temporal lobe epilepsy (TLE).
Method: A cross-sectional study was conducted on forty TLE patients during a neurological consultation in the day clinic based in Agadir, Morocco. Data were collected using an appropriate questionnaire designed for this study.
Results: the age of onset of seizures in 62.5 of the participants were below the age of 15 years. In addition, the time between the first seizure and the medical consultation was about 60 to 80 months for 62.5% of the participants. Again, 65% of participants presented with generalized and focal type seizures. Lastly, 40% of the seizures last between 2 to 5 minutes. Stress is the triggering factor of seizures that is most reported in 60% of participants. Additionally, the most lifted Aura types are vertigo and epigastric rising respectively by 40% and 30%. Moreover, half of the participants revealed post-critical symptoms such as fatigue, amnesia, myalgia, language disorder, and headaches.
Conclusion: the analysis of the semiology of the seizures affirms the specificity of the ELT. These results are useful for comprehensive and appropriate management.

1574
Resource limitations in general practice and family medicine

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Purpose: People with epilepsy (PWE) feel underserved by care in general practice and rely mainly on overstretched services in secondary care. The purpose of this presentation is to describe an educational package for generalists created in collaboration with Epilepsy Ireland

after surveying the experiences of PWE when visiting their general practitioner. By offering care in the community this can reduce pressures on hospital services. The key aspect of this work is in identifying the different educational objectives for this group as set out by patients. The presentation will be a useful opportunity to further test the validity of the package.
Method: An educational video package has been created for general practitioners in Ireland and the UK drawing on published guidance published though the Irish College of General Practitioners, the Royal College of GPs and a seminal work Managing Epilepsy in Primary Care (Taylor 1996) and the experiences of PWE.
Results:

1. General practice has sparse involvement in epilepsy care
2. There is a perception that GPs lack knowledge and confidence about epilepsy
3. PWE welcome guidance regarding GP consultations

The video addresses the following objectives:

- Managing seizures (control, frequency, type and date of last seizure)
- Anti-Seizure Medications (current dose, side effects, adherence, storage, and ordering)
- Treatment and personal safety plans
- Mood disorders and suicide risk
- Fertility, contraception and Pregnancy Prevention Programme
- Driving, safety at work, alcohol
- Provide lifestyle and diet advice to reduce osteoporosis
- Signpost PWE to Patient Groups such as Epilepsy Ireland

Conclusion: General practice is a setting that is not seen as providing care for PWE. There is an educational package based on identified objectives that can improve care in community settings.

1575
Healthrelated quality of life in patients with temporal lobe epilepsy

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Purpose: Temporal lobe epilepsy (TLE) predisposes to cognitive difficulties and social and psychological consequences. The evaluation of its impact on health-related quality of life (HRQOL) is necessary for the management of patients. The purpose of the study is to identify the correlated and predictive factors of a decrease in Healthrelated quality of life
Method: An institution-based cross-sectional study was conducted on forty patients with TLE during a neurological consultation in the day clinic based in Agadir, Morocco. The Quality of Life in Epilepsy Inventory-31 (QOLIE-31) was used to measure HRQOL. Multiple linear regression was fitted to assess the association between HRQOL and the sociodemographic, clinical, psychiatric, and cognitive variables. The P-value < 0.05 and a 95% confidence interval were used to declare statistical significance.
Results: The overall HRQOL score was 48.14 ± 22.02. Out of the seven scales, the Seizure worry scale score was the lowest. The self-esteem score, and Cognitive performance (MoCA) score were positively associated with HRQOL. whereas seizure duration, generalized seizure type, seizure frequency, Anxiety HADs score, and Depression HADs score were negatively associated with HRQOL. Finally, in the multivariate regression model: anxiety, depression, seizure frequency, and self-esteem explained approximately 78.9% of the variance in the overall QOLIE-31 score.
Conclusion: This study revealed that the HRQOL of patients with TLE was low. Numerous biomedical, psychological, and social factors influence the patient's HRQOL. These findings attest to the need for an integrated biopsychosocial model and a long-term perspective to improve the HRQOL of epilepsy patients.

1622

Intellectual disability is a very common co-morbid condition among children with previously untreated epilepsy in northern Nigeria

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Purpose: To determine the frequency of intellectual disability (ID) among children with previously untreated epilepsy in northern Nigeria.

Method: Children, ≥ 6 months and < 17 years, with previously untreated epilepsy were ascertained in three cities in northern Nigeria using a previously validated epilepsy screening and seizure classification tool in the local native language (Hausa) followed by diagnostic exams. Children with previously untreated epilepsy were enrolled in the *Bridging the Childhood Epilepsy Treatment Gap in Africa* (BRIDGE) non-inferiority cluster randomized clinical trial of task-shifted epilepsy care to community health workers. Children five years and older enrolled in the BRIDGE RCT were evaluated for ID by a qualified psychologist and/or psychiatrist, including use of the Raven's Coloured Progressive Matrices Test.
Results: 1134 children enrolled in BRIDGE ages 5 years and older were evaluated for possible ID: 135 children were designated as having "presumed profound ID" because of an absence of expressive and receptive language; 357 children were designated as having "presumed ID" because they were unable to complete the Raven's test and were determined by the psychologist and/or psychiatrist to have an uncertain level of ID; 310 were Grade 5 "Intellectually Impaired" (≤ 5th percentile); 115 were Grade 4 «Below Average»(<5th - ≤ 25th percentile); 69 were Grade 3 «Average» (> 25th - < 75th percentile); 86 were Grade 2 «Above Average» (75th - < 95th percentile); and, 62 were Grade 1 «Superior» (≥ 95th percentile). An additional 52 children could not be evaluated because of severe hyperactivity (18), frequent seizures (8), acute febrile illnesses (3), blindness (4), deafness (1), autism (6), choreoathetosis (2), and non-specific behaviors (10). There were no significant differences in testing outcomes between the two arms of the BRIDGE RCT.
Conclusion: Intellectual disability occurs among 70.7% of children 5 years and older with previously untreated epilepsy in northern Nigeria.

Epilepsy Surgery

1527

Thalamic interictal activity is associated with surgical outcome in focal epilepsies

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Purpose: Although the role of thalamus in epilepsy is now recognized and its stimulation is becoming more and more attractive in the treatment of drug-resistant epilepsies, only few data are yet available on thalamic interictal activity in these patients. The present study aims to investigate the thalamic interictal epileptogenic biomarkers and their association with clinical variables on a large cohort of patients explored by stereotactic-EEG (SEEG).

Method: We studied 121 patients (M/F=62/59; median age at SEEG=28, min-max=3-70) who underwent SEEG with thalamus implantation during pre-surgical evaluation for focal drug resistant epilepsy. For each patient, 10 minutes of rest and sleep SEEG records have been collected. First, we analyzed the thalamic interictal activities in SEEG records using Delphos, an automatic detector of Spikes and High Fast Oscillations (HFOs). Second, we studied the associations between interictal activities and clinical variables.
Results: Spikes and HFOs, including fast ripples, were detected in the thalamus during rest-waking periods and sleep recordings. We found higher rate of Spikes (Wilcoxon test, $p<0.01$) and HFOs (Wilcoxon test, $p<0.05$) in the thalamus only during sleep in patients with a poorer surgical outcome, evaluated by the persistence of invalidating seizures (Engel 3 and 4 vs Engel 2 and 1). No significant differences in interictal activity were found with respect to type, lateralization, aetiology of epilepsy, epileptogenicity of the thalamus (assessed by the Epileptogenicity Index).
Conclusion: Our work confirms the relevance of the study of the thalamus in the epileptogenic networks of focal epilepsies. Although not directly involved in the epileptogenic zone, the thalamus shows increased interictal activity (both Spikes and HFOs) in sleep in patients with a poor outcome compared to patients with a good outcome after surgery and/or thermocoagulations. Further analysis, including connectivity analysis, will emphasize the importance of this structure in focal epilepsies.

1540

Effect of hippocampal sclerosis level on memory score in mesial temporal lobe epilepsy patients after anterior temporal lobectomy

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Purpose: Determine the effect of the level of hippocampal sclerosis on changes in memory scores between pre and post-surgery.
Method: This was a retrospective study on mesial temporal lobe epilepsy (MTLE) patients who had anterior temporal lobectomy (ATL) at Kariadi or Telogorejo Hospital, Semarang, Indonesia during the 2018-2021 period. Subjects were divided into 2 groups; severe and mild HS. Severe HS was determined if the percentage of gliosis or neuronal reduction in cornu ammonis 1 and 4 exceeded 80%, while mild if less than 80%, Both groups underwent memory examination including verbal and visual task, recall, and recognition memory with pre- and post-operative examination interval ranging from 1 to 4 years.
Results: The study subjects were 54 people with 29 people with severe sclerosis and 25 people with mild-moderate clerosis. The level of hippocampal sclerosis had a significant effect ($p = 0.027$) on changes in post-surgery verbal task memory scores with an RR of 1.793. There

were no significant effects of the level of hippocampal sclerosis on verbal recall memory scores (p = 0.951), verbal recognition (p = 0.202), visual construction (p = 0.643) and construction recall (p = 0.319).
Conclusion: There was an effect of the level of hippocampal sclerosis on changes in verbal task memory scores in post-LTA ELTM patients. Patients with severe hippocampal sclerosis have a 1.793 times higher risk of increasing verbal task memory compared to patients with mild hippocampal sclerosis.

1643

Disparities in access to epilepsy surgery care in children with drug-resistant epilepsy: implications for long-term survival outcomes

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Purpose: Our recent publication in Lancet Child and Adolescent Health examined long-term survival rates for pediatric patients with drug-resistant epilepsy (DRE) treated with antiseizure medications (ASMs) only, ASMs plus vagus nerve stimulation (VNS), and ASMs plus cranial epilepsy surgery in a large United States (US) administrative database. The difference in survival probabilities was statistically significant (p<.001). Adjusted probabilities of survival beyond 10 years were 89.27% for the ASMs only cohort (95%CI, 87.71%-90.85%), 92.65% for VNS cohort (95%CI, 90.62%-94.72%), and 98.45% for cranial surgery cohort (95%CI, 97.53%-99.38%). In this study, we examined factors associated with higher likelihood of receiving surgical treatment (VNS or cranial epilepsy surgery).
Method: Patients aged 0-17 years with DRE between 01/01/2004-31/12/2020 were identified from the Pediatric Health Information System data set across 49 US pediatric hospitals. Patients treated with ASMs only or ASMs plus VNS or ASMs plus cranial epilepsy surgery were included. Chi-square tests determined associations between treatment time and preoperative factors such as treatment type, age, sex, race/ethnicity, insurance type, geographic region, epilepsy type, and medical complexity (presence of pediatric complex chronic conditions [PCCCs]).
Results: 18,292 total patients were included: 10,240 patients treated with ASMs only, 5,019 patients with ASMs plus VNS, 3,033 patients with ASMs plus cranial epilepsy surgery. There were significant differences in age, geographic region, race/ethnicity, presence of PCCCs, diagnosis, and insurance type (p < 0.001). Those treated surgically, either with VNS implantation or cranial epilepsy surgery, were 2 years older than ASMs only. ASMs only patients were less likely to be reported as non-Hispanic white (51.78%), less likely have a focal/partial epilepsy diagnosis (8.74%), and less likely carry private medical insurance (35.82%).
Conclusion: We show a link of disparities in pediatric epilepsy surgery care and survival outcomes. Focused strategies are needed to expand access to comprehensive epilepsy care with

neurosurgical evaluation and offerings when appropriate.

Genetics

1436

Genetic variants in childhood-onset developmental and/or epileptic encephalopathy identified by clinical exome sequencing and its role in clinical care: experience from a tertiary care centre

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Purpose: Background: Genetic factors in epilepsy play a major role in aetiology of developmental and/or epileptic encephalopathy(D/EE). It contributes not only as a diagnostic tool but is crucial to develop molecular targeted medications, clinical referrals, genetic counselling, and anticipatory guidance.
Objective: To identify spectrum of genetic variants in a paediatric cohort with D/EE of unknown aetiology and to study its role in various aspects of clinical care.
Method: We conducted clinical exome sequencing of almost 6000 epilepsy candidate NGS gene panel in 68 children aged 1-15 years with clinical and electrophysiological diagnosis of a D/EE of unknown aetiology.
Results: 27 children with LGS phenotype, 28 with D/EE-SWAS ,8 cases of GEFS+/Dravet spectrum , 2 cases with Myoclonic-Atonic Epilepsy, one with sleep-related hypermotor epilepsy, one with Early onset Absence Epilepsy (EOAE), one with Epilepsy and Myoclonic Absences were included. We yielded pathogenic/likely pathogenic variants in 18 out of 68 subjects (26%) in the known epilepsy genes,some of them are: CDKL5, SCN1A, CDH15, SYNGAP1, SLC69A6, WWOX, DEPDC5. Three out of eight in the Dravet/ GEFS plus spectrum tested positive - two cases of SCN1A, 1 case of ADGRV. There were three cases with pathogenic variants for neurodevelopmental disorders SMARCA2, LINS1 and MLC1.
Conclusion: In addition to its role as a diagnostic tool, genetic testing is also crucial in other aspects of clinical care. We successfully treated a toddler with gain of function variant in KCNA2 presenting as EOAE with Acetazolamide and identified a child with 22q11.21 mutation who responded well to calcium supplementation. Anticipatory guidance could also be provided in terms of prognosis, referrals and genetic counselling.

1451

GET' complements Genes4Epilepsy: an application (gene, epilepsy, treatment)

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Purpose: We aimed to take advantage of Genes4Epilepsy (an epilepsy gene resource) as a reliable source to develop an advanced version of GET application (GET prime).
Method: We downloaded the list of all 954 epilepsy-related genes that are included in Genes4Epilepsy. MEDLINE was searched for the related publications for each gene from the inception until 1 April, 2023. These key words were used: “epilepsy” AND “gene name” and also “seizure” AND “gene name”. Human studies, reviews, guidelines, and any other publication with information on the specific treatments related to any given specific gene in humans were included. Animal studies and any other non-human study (e.g., in vitro studies) were excluded. Genes with specific treatment strategies were included in the database.
Results: A database of 137 genes, that are associated with various syndromes and for which specific treatment strategies exist, was developed. A web-based application (a search engine) was developed based on the above-mentioned database (GET prime); this is freely available at http://getprime-sums.com.
Conclusion: Based on Genes4Epilepsy and the available publications, a web-based application was developed as a simple search engine “GET (Gene, Epilepsy, Treatment) prime”. This is an application to facilitate the decision-making process for the treating physician. However, this application should not be regarded as a practical App for routine use yet. A group of experts (e.g., geneticists, pediatric and adult epileptologists, endocrinologists, dieticians, etc.) should provide the level of evidence for hundreds of the publications on these 137 genes and this website should be validated by clinicians and by input from experts in the field.

1469

Gene panel analysis of resected brain tissue in epilepsy surgery patients: a pooled-data analysis of 483 patients

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Purpose: Malformations of cortical development (MCDs) are common causes of refractory epilepsies subjected to surgery. We aimed to provide an overview of germline and somatic variants in a multicenter cohort of resective epilepsy surgery patients.
Method: We included patients who underwent epilepsy surgery between 2004 and 2020, as reported by 3 previously published cohort studies (from France; FR, Korea; KR, and the USA), combined with a similar cohort from the Netherlands (NL). All patients had an established histopathological diagnosis of mMCD, MOGHE, FCD, HME, or had no lesion. Gene panel analysis of resected tissue and available blood/saliva samples was performed to search for somatic and germline variants, respectively.
Results: In 483 epilepsy surgery patients genetic analysis of resected tissue was performed. Blood or saliva samples were available in 73% (353) of patients. Tissue analysis yielded a pathogenic variant in 66% (108) of FCD II cases and 77% (23) of HME cases, mainly in mTOR pathway genes, and in 28% (33) of FCD I/mMCD/MOGHE cases, mainly concerning *SLC35A2* variants. Ten percent (7) of patients without a histopathological lesion had a *SLC35A2* (5)*, NPRL3* (1)*,* or *DEPDC5* (1) pathogenic variant. Somatic mutations, two-hit mutations, and germline mutations accounted for 29% (139), 2% (8), and 5% (24) of all patients, respectively. Most pathogenic somatic mutations (59%, 87 of 147) had a variant allelic frequency (VAF) below 5%..
Conclusion: This study shows that genetic findings varied according to epileptogenic pathology, with FCD II/HME patients having the highest proportion of somatic, mostly mTOR mutations, while FCD I/mMCD/MOGHE and non-lesional tissue predominantly revealed *SLC35A2* mutations. Deep sequencing of epilepsy brain tissue in patients with and without a presurgical germline genetic diagnosis may provide valuable prognostic information. Further analysis of the correlation between genetic variants and surgical outcomes in these cohorts, will improve patient counselling and postoperative treatment decisions.

1494

Genome-wide analyses reveal shared genetic architecture underlying common epilepsies and cortical morphology

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Purpose: Epilepsy is associated with alterations in brain cortical morphology. However, the question of whether cortical differences in individuals with epilepsy are a result of the condition itself, its treatment, or serve as its cause remains elusive. Both epilepsy and cortical morphology are heritable, but to what extent genetic variants contribute to brain abnormalities in epilepsy is poorly understood. Here, we aimed to determine the degree of shared genetic architecture between common epilepsies and cortical thickness (CRT-TH) and cortical surface area (CRT-SA) to identify overlapping genetic loci.
Method: We analyzed genome-wide association study data from a total of 139,942 individuals for epilepsies (all epilepsy, focal epilepsies and genetic generalized epilepsies from ILAE), CRT-TH and CRT-SA using Gaussian mixture modeling analysis (MiXeR) and the conjunctional false discovery rate (conjFDR) to identify genetic overlap. The identified loci were functionally annotated using a variety of biological resources.
Results: We found that CRT-SA (1.8K causal variants) and CRT-TH (1.3K causal variants) are less polygenic compared to epilepsies (2.4K to 2.9K causal variants), with extensive overlap between CRT-SA and genetic generalized epilepsy (GGE) (1.1K), all epilepsy (1.1K) and juvenile myoclonic epilepsy (JME) (0.7K), and between CRT-TH and GGE (0.8K), and all epilepsy (0.7K) and JME (0.8K) despite weak or no genetic correlations. Using conjFDR, we identified GGE loci jointly associated with CRT-SA (15), and CRT-TH (15). We also found shared loci between CRT-SA and childhood absence epilepsy (3), and CRT-SA and JME (6). We discovered novel loci for CRT-TH (10), CRT-SA (14), GGE (21), JME (2), and childhood absence epilepsy (2). The shared loci had mixed effect directions.
Conclusion: Our findings demonstrate extensive genetic overlap between genetic generalized epilepsies and cortical morphology, suggesting a complex genetic relationship with mixed effect directions. The findings further suggest that shared genetic variants may contribute to cortical alterations in patients with epilepsy.

1503

Expansion of the set of seizure-associated copy number variants to 25 and their clinical characterization in 562 carriers

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Purpose: We aimed to identify recurrent copy number variants (CNVs) associated with epilepsy and to characterize the clinical features of carriers.
Method: We compared CNV data from 26,699 people with seizure disorders with those from 492,324 controls, identifying loci associated with seizure disorders. Using a Bayesian algorithm, we identified minimal credible intervals with 95% confidence of containing the causal elements at each locus. Then we identified people carrying these CNVs among 10,880 participants in the Epi25 Collaborative study (years 1–3) and described their detailed clinical features using the Human Phenotype Ontology, with 214,203 annotations spanning 1,667 clinical features. We tested CNV-phenotype associations using Fisher's Exact Test with MinP adjustment for multiple dependent hypothesis tests and performed phenotypic similarity analysis.
Results: We identified 25 CNVs (22 novel) enriched among people with seizure disorders, containing 33 credible intervals. Both deletion and duplication were found at three loci.
In Epi25, 562 individuals (5.2%) carried at least one seizure-associated CNV. Deletions at 15q13.2-q13.3 and 22q11.21 were characterized by features of generalized epilepsy, duplications at 22q11.21, 9q34.3 and 16p11.2 with focal epilepsy, and deletions at 1p36.33 and 15q12-q13.1 with features of developmental and epileptic encephalopathy.
Across 32 detected CNV credible intervals, we identified 622 nominally significant associations with 19 remaining significant after adjustment for multiple testing. For example, deletion at 2p21-p16.3 (the most common CNV, carried by 1.0%) was associated with generalized tonic-clonic seizures (odds ratio, OR=2.3, $p<0.02$) and negatively with focal-onset seizures (OR=0.46, $p<0.009$). Duplication at 16p11.2 (0.074%) was associated with non-epileptic seizures (OR=82, $p<0.03$).

Conclusion: Analysis of large cohorts has allowed us to increase the number of CNVs associated with seizure disorders, cumulatively finding these in 1 in 20 people with non-acquired epilepsies. Our high-resolution analysis of phenotypes informs clinicians of the clinical features that people carrying these variants are at particular risk of encountering.

1505

Genome-wide meta-analysis of over 29,000 people with epilepsy reveals 26 loci and subtype-specific genetic architecture

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Purpose: Despite previous large-scale genomic studies, much of the heritability of epilepsy remains unaccounted for. Here we aimed to identify novel epilepsy risk loci and to elicidate the complex genetic architecture of epilepsy subtypes to provide insights into the underlying pathophysiology.
Method: In a massive collaborative effort, we performed a trans-ethnic genome-wide association study (GWAS), including 29,944 cases, stratified into three broad- and seven sub-types of epilepsy, and 52,538 controls. After rigorous quality control, we used a combination of ten in silico prioritization methods to pinpoint the most likely causal gene in each epilepsy risk locus, and we performed analyses to assess which brain tissues, cell types and biological pathways were most likely to be involved. We performed SNP-based heritability analyses to determine the proportion of epilepsy risk attributable to common genetic variants. Furthermore, we aimed to identify novel drugs with predicted efficacy when repurposed for the treatment of epilepsy.
Results: We identify 26 genome-wide significant loci, 19 of which are specific to genetic generalized epilepsy (GGE). We implicate 29 likely causal genes underlying these 26 loci. SNP-based heritability analyses show that common variants explain between 39.6 and 90% of genetic risk for GGE and its subtypes. Subtype analysis revealed markedly different genetic architectures between focal and generalized epilepsies. Gene-set analysis of GGE signals implicate synaptic processes in both excitatory and inhibitory neurons in the brain. Prioritized candidate genes overlap with monogenic epilepsy genes and with targets of current anti-seizure medications. Finally, we leverage our results to identify alternate drugs with predicted efficacy if repurposed for epilepsy treatment.
Conclusion: We uncovered several novel epilepsy risk loci and provide pathophysiological insights that could aid targeted therapy of epilepsy.

1516

The effect of gluten sensitivity based on HLA genotyping on the drug therapy of

epilepsy

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Purpose: Gluten sensitivity (GS) is over 2 times more prevalent in patients with epilepsy compared to the general population. It is also known that 99% of GS were genetically predisposed through the human leukocyte antigen. The purpose of this study was to investigate whether underlying GS based on HLA genotyping have an effect on the drug therapy of epilepsy.
Method: A case-control study was conducted on 50 epileptics and 50 normal adults matched for age, gender, and race. Those who had gastric surgery, treatment for H. pylori, history of antibiotic or steroid drug use within 4 weeks of enrolment were excluded. The blood samples were sent for HLA-DQ 2.2, DQ 2.5, DQ 7 and DQ 8 genotyping. Those positive for any one or more of the HLA -DQ genotypes were considered to have GS. The number of antiseizure medications (ASM) given to all patients were recorded.
Results: Our study showed that HLA-DQ 2.2 was seen in 9 out of 50 epileptic patients and none in the control group (p: 0.003). However, the prevalence of HLA-DQ 8 was similar in both groups (18 in the epileptic group and 19 in the control group) and the HLA-DQ 2.5 and HLA-DQ 7 were not seen in both groups. Interestingly, 8 epileptics who were positive for both HLA-DQ 2.2 and HLA-DQ 8 (strongly positive) required more than one ASM for seizure control (p: 0.006).
Conclusion: Out of the four HLA-DQ genotypes, the strongly positive patients (i.e) HLA-DQ 2.2 and DQ 8 positive required multiple ASM for seizure control. This may suggest a possibility of malabsorption as a factor in the causation of the refractoriness to ASM and a possible benefit from a gluten free diet. Moreover, from this preliminary study we can suggest a HLA genotyping to be routinely tested for those patients requiring multiple ASM.

1541

Early-infantile developmental and epileptic encephalopathy (EIDEE) associated with *CASK* gene mutation

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Purpose: Presentation of a clinical case of a patient with early-infantile developmental and epileptic encephalopathy (EIDEE), dysmorphisms, structural brain alterations, and other associated clinical conditions.

Method: Case report based on clinical, neuroimaging, exome, and electroencephalographic data.
Results: Male patient, 5 months old, with non-consanguineous parents and no gestational complications. At birth, he presented with hypotonia, apnea and dismorphic features (micrognathia, high palate, redundant right auricular lobe, low hairline, hands in flexion with extended fifth finger, clubfoot with prominent fetal pads, hyperconvex nails, hypoplastic bilateral fifth toenail, poor/absent plantar and palmar creases, sacral dimple, and micropenis). Neurological examination revealed revealed microcephaly (31.5 cm), axial hypotonia and appendicular hypertonia, hypoactive deep tendon reflexes, weak sucking reflex, and absent cochleopalpebral reflex. He had sensorineural hearing loss, glossoptosis, swallowing disorder, lack of airway protection, gastroesophageal reflux, and laryngomalacia, leading to gastrostomy and tracheostomy placement. Cranial MRI showed marked cerebellar volume reduction and diffuse thinning of the brainstem. Throughout the hospitalization, he experienced central apnea events and several septic episodes of different infectious foci. At 33 days old, he started multiple and sequential epileptic seizures. Video-electroencephalogram revealed burst-suppression pattern, multifocal and generalized interictal abnormalities, myoclonic, spasms, and tonic seizures, as well as various jerks without electrographic correlation. The clinical condition was consistent with EIDEE. Several medications were attempted (phenobarbital, levetiracetam, clobazam, pyridoxine, carbamazepine, vigabatrin, and prednisolone). Finally, ketogenic diet resulted in improvement of burst-suppression pattern, but without evident clinical improvement, and was discontinued due to refractory vomiting. Exome sequencing revealed a likely pathogenic *de novo* variant c.2630T>G in hemizygosity in the *CASK* gene.
Conclusion: CASK disorders include a spectrum of phenotypes, including microcephaly with pontine and cerebellar hypoplasia (MICPCH) accompanied by severe epileptic encephalopathy, which is consistent with the presented case. However, the dysmorphic features observed in this patient have not been commonly described in the literature.

1545

Neonatal developmental and epileptic encephalopathy with movement disorders and arthrogryposis (NDEEMA) – novel common phenotype across brain-expressed sodium channelopathies

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Purpose: Neonatal developmental and epileptic encephalopathy with movement disorders and arthrogryposis (NDEEMA) recently was described as the most severe end of the gain-of-function *SCN1A* disorder spectrum. We aimed to explore if NDEEMA is a common phenotype across all brain-expressed sodium channelopathies (*SCN2A, SCN3A* and SCN8A).
Method: Patients with NDEEMA due to pathogenic variants in *SCN2A, SCN3A* or *SCN8A* were identified through a systematic literature search, internal databases or an international network of epileptologists/geneticists. Furthermore, a systematic literature search was performed to review studies describing functional characteristics of the identified variants.
Results: We identified 14 patients across different sodium channels who presented with NDEEMA (*SCN1A* (1), *SCN2A* (4), *SCN3A* (1), *SCN8A* (8)). Variants corresponding to *SCN1A*-NDEEMA variants were identified in 6 individuals, while novel variants were found in the remaining seven. 6/14 individuals are deceased. All patients had congenital arthrogryposis affecting either the upper, lower, or multiple limbs. 10/12 liveborn individuals had prenatal/neonatal onset epilepsy with tonic seizures and apneas. 2 individuals died on the first days of life and did not develop seizures. All patients developed movement disorders within the first years of life, with myoclonus, dystonia, and tremor being the most common. MRI was available in 6 subjects, showing cortical/subcortical atrophy, thinning of corpus callosum, and delayed myelination. Dysmorphic features were observed in 10 individuals, including: congenital hernias, hydrocele/cryptorchidism, low set/dysmorphic ears, micrognathia. Sodium channel blocker treatment decreased seizures in a subset of patients.
Functional characteristics review of the identified variants revealed that 9 variants had been previously functionally tested: 8 had an overall gain-of-function and 1 variant had a mixed gain- and loss-of-function effect.
Conclusion: Our study expands the spectrum of gain of function *SCN2A/SCN3A/SCN8A*-related epilepsy phenotypes to include neonatal developmental and epileptic encephalopathy with movement disorder and arthrogryposis. Further studies are needed to clinically characterize this phenotype and understand its pathogenesis.

1549

Effect of *SCN1A* intronic variants on Na_v**1.1 protein expression and sodium channel function and its correlation with epilepsy phenotype severity**

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Purpose: To investigates the effect of intronic variants in the SCN1A on mRNA splicing, protein expression, and electrophysiological properties of sodium channels, as well as their correlation with epilepsy severity.
Method: Two variants, c.4853-1 G>C (canonical splice site) and c.4853-25 T>A(deep intronic region), were identified in intron 25 of SCN1A, which were associated with severe Dravet syndrome (DS) and mild focal epilepsy with febrile seizures plus (FEFS+), respectively. pCMV-SCN1A-WT was used as template to construct mutant plasmids and transfect HEK-293T cells. Western blotting and confocal laser microscopy were used to analyze the protein expression in the cell membrane and its subcellular distribution. The whole-cell patch clamp technique was used to assess the electrophysiological function of sodium channels.
Results: The mutant led to the expression of truncated Nav1.1 proteins (Mu4853-1: c.4853-1 G>C/p. G1618-I1625del,and Mu4853-25: c.4853-25 T>A/p. G1618VfsX1625) with the predicted molecular weights. Compared with the WT Nav1.1, G1618-I1625del and G1618VfsX1625 expression on the cell membrane was reduced ($p=0.008$ and $p<0.001$, respectively), but the expression of the former was significantly higher than that of the latter ($p<0.001$). More truncated proteins were retained in the cytoplasmic endoplasmic reticulum, with lower fluorescence on the cell membrane ($P=0.013$ and $P<0.001$, respectively); notably, G1618-I1625del expression was significantly higher than G1618VfsX1625 ($P<0.001$). Both mutants attenuated sodium currents ($P<0.01$), and the activation speed of the voltage-dependent half activation potential was slowed ($P<0.01$),leading to partial loss of sodium channel function (pLOF). However, the FEFS+-related mutant had a faster inactivation rate than the wild type, while the DS-related mutant did not differ significantly.
Conclusion: dominant-negative effects may lead to severe phenotypes caused by splice site variants, while haploinsufficiency is a possible cause of milder phenotypes caused by deep intronic variants. Differences in protein expression levels and altered electrophysiological properties of sodium channels are important reasons for differences in epileptic phenotypes.

1558

Polymorphism of glucocorticoid receptor gene (rs41423247) in functional seizures

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Purpose: We investigated the association between the glucocorticoid receptor (GR) gene, also known as the nuclear receptor subfamily 3, group C, member 1 (NR3C1), rs41423247 polymorphism and functional seizures (FS) in a case-control study. We hypothesized that the tested polymorphism has significant associations with FS independent from comorbid depression.
Method: Seventy patients with FS, 70 with major depressive disorder (MDD), and 70 healthy controls (HC) were studied. Their DNAs were analyzed for NR3C1 rs41423247 polymorphism.

Results: Genotype and allele frequencies of rs41423247 were different between the three groups. G allele carriers were more frequent in FS patients and those with MDD compared to healthy controls (P=0.0001). However no significant difference was observed with respect to allele distributions between FS and MDD groups (P=0.391). People with CC genotype were less often predisposed to FS (FS *vs.* HC: Codominant model; P=0.001, OR= 0.11, 95% CI=0.05-0.24, and -2loglilkelihood=231.7). In comparison between FS group and other (MDD+HC) groups, we observed the predisposing role of CG genotype to FS (Codominant model; P=0.001, OR=5.63, 95% CI=2.60-12.40 and -2loglikelihood=245.99).
Conclusion: Patients with FS and those with MDD were significantly more often G allele carriers in rs41423247 compared with healthy controls. However, we could not exclude the possibility of existence of confounding effects of depression. Future genetic studies of patients with FS should include a comparison group with depression in addition to a comparison group of healthy controls.

1561

Coexistence of temporal lobe epilepsy and idiopathic generalized epilepsy

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Purpose: We investigated the frequency of coexistence of focal epilepsy [temporal lobe epilepsy (TLE), in particular] and idiopathic generalized epilepsy (IGE) in a retrospective database study. We also explored the underlying pathomechanisms of the coexistence of TLE and IGE based on the available information, using bioinformatics tools.
Method: The first phase of the investigation was a retrospective study. All patients with an electro-clinical diagnosis of epilepsy were studied at the outpatient epilepsy clinic at Shiraz University of Medical Sciences, Shiraz, Iran, from 2008 until 2023. In the second phase, we searched the following databases for genetic variations (epilepsy-associated genetic polymorphisms) that are associated with TLE or syndromes of IGE: DisGeNET, genome-wide association study (GWAS) Catalog, epilepsy genetic association database (epiGAD), and UniProt. We also did a separate literature search using PubMed.
Results: In total, 3760 patients with epilepsy were registered at our clinic; four patients with definitely mixed focal epilepsy and IGE were identified; 0.1% of all epilepsies. We could identify that rs1883415 of ALDH5A1, rs137852779 of EFHC1, rs211037 of GABRG2, rs1130183 of KCNJ10, and rs1045642 of ABCB1 genes are shared between TLE and syndromes of IGE.
Conclusion: While coexistence of focal epilepsy (TLE in particular) and IGE is a rare phenomenon, this could be explained by shared genetic variations.

1564

The photoparoxysmal response belongs to the spectrum of electroencephalograph-

ic findings in patients with triple X syndrome and epilepsy

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Purpose: A recent publication [Dell'Isola et. al, Seizure 2022] has shed light on the features of epilepsy in triple X syndrome. We'd like to comment on the topic bringing our personal experience.
Method: Over the last 10 years, we have been following-up 3 children with triple X syndrome and epilepsy performing periodic prolonged EEG monitoring and clinical evaluation.
Results: **Patient 1** was referred at 5 years of age for Focal-Impaired-Awareness Seizures (FIAS), with possible evolution to bilateral tonic-clonic seizures. EEG captured asynchronous centro-temporal and temporo-parieto-occipital interictal spikes and atypical absence seizures with generalized slow spike-and-wave discharges. She displayed an overt photoparoxysmal response (PPR). By switching from carbamazepine to valproate we obtained seizure freedom and PPR disappearance. **Patient 2** developed FIAS at 2 years of age possibly evolving to bilateral convulsive seizures. The EEG depicted interictal temporo-parieto-occipital sharp waves and PPR, which remitted along with seizures soon after valproate introduction. Nine years later the PPR has reappeared, yet seizure freedom is ongoing. **Patient 3** at 8 years of age developed prolonged FIAS. Alike the other Patients, she exhibited temporo-parieto-occipital interictal discharges as well as a PPR. Valproate promoted seizure freedom, yet the PPR is still present at age 16-year-old.
Conclusion: Our observations confirm the prognosis of epilepsy is favourable in triple X syndrome and valproate is particularly effective. In all Patients we found PPRs that to our knowledge have never been reported in trisomy X. Epileptiform discharges were self-limiting, there were no associated symptoms or photic-induced seizures. Our findings need confirmation in larger samples and cannot be generalized to patients with triple X who develop seizures devoid of occipital features. However, we suggest to carefully investigate the effect of intermittent photic stimulation during follow-up as PPR might represent a proper endophenotype in a subset of Patients with trisomy X.

1601

CNVs in refractory epilepsy – a diagnostic odyssey!!

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Purpose: Data regarding pathogenic copy-number-variants(CNVs) as attributed causes of

refractory-epilepsy in childhood and developmental-epileptic-encephalopathies(DEE) from Indian subcontinent is lacking.
Aims: To determine the yield and electro-clinical profile of the epilepsy patients with CNVs
Method: This data is derived from a prospectively maintained cohort of refractory-epilepsy patients of uncertain etiology from a tertiary referral centre for epilepsy in South India. Data of all the patients with refractory-epilepsy who underwent genetic testing was reviewed. Patients with CNVs were identified and their electroclinical profile was elucidated. Subjects with aneuploidy were excluded.
Results: Of 504 patients who underwent genetic testing, 41 patients(males 24; 4months-15 years age) had CNVs[detected by Chromosomal-microarray(CMA) in 10, clinical/whole exome-sequencing(CES/WES) in 28, MLPA in 2, FISH in 1] with deletions in 20, duplications in 20, 1 patient had 1 deletion and duplication. CNVs size ranged from 311bp to 19.8mb. Most commonly CNVs were seen in Chr 2 and 15 in 7(17%) patients each, with hotspots being 15q11 in 5(12%) followed by Xp22, 22q11 in 3(7.3%) each. CNVs were pathogenic in 11(26.8%), likely-pathogenic in 8(19.5%) while remaining were promising VUS(22; 53.6%). Initial development was normal in 7(17%), while 30(73%) had delay. 9(21%) had developmental regression after seizure onset. 17 had facial dysmorphism and 10 had family history of seizures or neurodevelopmental disorders. Seizure onset was neonatal in 2, infantile in 21, early childhood(<5years) in 11, late childhood or adolescence in 7. Epilepsy syndromes reported were focal in 13, generalised in 7, Dravet in 5, West in 5, LGS in 4, CSWS in 3, unclassifiable-DEE in 3 and Ohtahara in 1. Pathogenic/likely-pathogenic CNVs were detected in 3.5% of CES/WES tests and 26.9% of CMA tests.
Conclusion: This is the largest series from India on CNVs in epilepsy. The study supports use of exome-sequencing to supplement CMA in detecting CNVs in drug-resistant childhood epilepsy of uncertain etiology.

1619

Early-onset absence epilepsy and photoparoxysmal EEG response related to a novel missense YWHAG variant

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Purpose: YWHAG gene is located on chromsome 7q11.23 and encodes for the highly brain-expressed protein 14-3-3γ. Defects in heterozygosity of the gene cause a very rare condition called developmental and epileptic encephalopathy (DEE) 56. 30 cases have been described in the literature, of these only 18 are well described with detailed clinical mani-

festations. YWHAG deficiency is characterized by early-onset epilepsy, mild-moderate intellectual disability, mild-moderate motor and language developmental delay, autism spectrum disorder, ADHD, in the presence of mostly nonspecific neuroradiological changes.
Method: Description of a clinical case of YWHAG gene mutation with particular attention on epileptological, EEGgraphic, neuropsychological, and neuroradiological characterization
Results: A 12-year-old patient with early onset absence epilepsy associated to eyelid myoclonia well controlled by ethosuximide and levetiracetam, mild intellectual disability and expressive speech disorder. Video-EEG recordings showed generalized epileptic spike and polyspike discharges and photoparoxysmal response to intermittent photic stimulation. MRI evidenced mild brain asymmetry due to less development of the posterior region of the right hemicranium. Whole exome sequencing analysis identified a pathogenic (de novo) variant in heterozygosity c.394C>G (p.Arg132Gly) of the YWHAG gene
Conclusion: Mutations in the YWHAG gene are associated with a highly heterogeneous clinical phenotype. Our case expands the spectrum of variants known to date and the phenotypic spectrum of the disease, particularly associated with the highlighted photoparoxysmal response. In light of the above, we believe it is important to include this mutation in the molecular study of patients with a compatible clinical manifestation.

1623

The diagnostic yield and treatment implications of whole-exome sequencing in pediatric epilepsies from a tertiary care hospital – a retrospective observational study

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Purpose: The objective of the study was to determine the yield of whole-exome sequencing in childhood epilepsies presenting to a tertiary care hospital in India.
Method: The clinical and diagnostic details of all new cases of children aged 1 month – 18 years presented with epilepsy to our hospital from January 2022 to April 2023 were collected from the hospital records. Those who underwent whole exome sequencing were included in the analysis. Those identified with variants of uncertain significance (VUS) underwent reverse phenotyping and were offered parental testing in relevant situations.
Results: A total of 784 children were diagnosed with epilepsy during the study period. 527/784 (67.2%) patients were diagnosed with self-limited childhood epilepsies, idiopathic generalized epilepsies, and structural epilepsy. 257/784 (32.7%) patients had suspected genetic etiology and were offered genetic testing and counseling. 156/257 (60.7%) with suspected genetic etiology underwent whole exome sequencing. Out of the 156, no pathogenic variants were identified in 31(19.8%), 69(44.2%) had variants of unknown significance (VUS), and reverse phenotyping or parental testing was not conclusive of pathogenicity. 56/156 had a pathogenic or likely pathogenic mutation accounting for an overall yield of 35.8% in our study population. Out of the 56, 20(35.7%) had developmental epileptic encephalopathy,

16(10.2%) had epileptic encephalopathy, 8(14.2%) had genetic syndromes and 12(21.4%) had channelopathies and metabolic pathway defects. 14/56 (25%) who had positive genetic testing were treated with precision therapies accordingly and obtained considerable seizure reduction and freedom.
Conclusion: The yield of whole exome sequencing in pediatric epilepsies with suspected genetic etiology was comparable to similar studies in the literature. Deciphering the genetic diagnosis is inevitable for providing precision therapies and improving outcomes.

Neuroimaging

1473

Value of PET /MRI co-registration in decision-making for patients with drug resistant epilepsy, Egyptian Study

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Purpose: Drug resistant epilepsy (DRE) is a devastating condition with various socioeconomic impact ranging from 15 to 60%. However, accurate detection of epileptogenic focus is challenging. As electroencephalograph(EEG) sensitivity is low, Magnetic resonant imaging (MRI) brain may be non-conclusive, we assessed the benefit of MRI/PET Co-registration in epileptogenic focus detection.
Method: An observational cross sectional analytical study in 40 people with epilepsy (PWE) with focal onset epilepsy according to ILAE classification 2017. All patients underwent detailed history taking and examination,MRI brain scan with epilepsy protocol, Ictal/Interictal EEG study, MRI brain scan with epilepsy protocol, and interictal PET/CT study.
Results: Our study showed that EEG either ictal or interictal could lateralize and/or localize in 22/40(53.6%) patients. MRI epilepsy protocol was lesional in 29/40(73.2%) patients. While PET brain could detect lateralizing and/or localizing hypometabolism in all patients. Patients were categorized into 3 groups.
First: All assessment modalities (clinical semiology and EEG with MRI brain) were concordant in 12(30%) patients, and PET were concordant to them.
Second: non-concordance between different assessment modalities that included 17 patients, PET had additional value and achieved concordance with other assessment modalities in 4(10%) patients; but failed in 13(32.5%) patients.
Third: patients with MRI brain negative (11patients), PET showed concordance with clinical

semiology and EEG in 6(15%) patients.
Conclusion: Multimodality approach with PET/MRI co-registration helped markedly in localization and further in proper decision-making in patients with focal onset DRE.

1484

Language-related network changes predict language performance in temporal lobe epilepsy: evidence from graph-based analysis

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Purpose: Temporal lobe epilepsy (TLE), as a network disorder, modifies the language-related network organization (Balter et al. Brain Lang 2014;193:31-44) and affects language functions (Hoppe et al. Epilepsia 2007;48 Suppl 9:26-29). However, studies that associate reorganizational changes and language performance are scarce (Bernhardt et al. Epilepsy Behav 2015;50:162–170). We explored whether graph-based network changes predicted language performance in people with TLE.
Method: We collected task-based fMRI data with sentence completion from 19 healthy controls and 28 people with left TLE. We evaluated small-world propensity and total network integration; segregation into modules and the integration within modules; the number and location of connector hubs, and tested whether these metrics differed between groups. We correlated these metrics to language performance in people with TLE.
Results: The language-related network was characteristic of a small world but differently segregated in the groups. People with TLE exhibited a module in the left temporal lobe, reflecting hyperconnectivity within the epileptic focus, but no module consisting of left perisylvian regions. There was a trend towards a higher difference between the total network integration and the intramodular integration (IS) in TLE (controls: M = -0.06, SD = 0.03; people with TLE: M = -0.08, SD = 0.04), $t(45) = 2.3$, $p = .02$. The reduction in IS with epilepsy duration predicted lower response accuracy ($\beta = 465.5$, $SE = 164.7$, $t(14) = 2.8$, $p = .01$). The increase in the number of connector hubs in the right hemisphere, in turn, was compensatory in TLE (controls: M = 3.1, SD = 1.2; people with TLE: M = 4.7, SD = 1.7), $t(45) = -3.5$, $p < .001$.
Conclusion: Our study revealed specific changes in network segregation and integration. It demonstrates reduced global connectivity and confirms compensation across the healthy hemisphere, consistent with previous epilepsy research.

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Lateralizing value of resting-state functional MRI in mesial temporal lobe epilepsy associated with hippocampal sclerosis

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Purpose: Hippocampal sclerosis (HS) is a common pharmacoresistant epilepsy condition requiring validation of the unilaterality and lateralization of the Epileptogenic Zone (EZ) before surgery. Our objective was to assess the reliability and reproducibility of independent component analysis applied to resting-state functional MRI (rs-fMRI) for lateralizing the EZ in the context of presurgical multimodal evaluation in a cohort of adult patients diagnosed with pharmacoresistant temporal lobe epilepsy associated with HS.
Method: This study included 29 adult patients with HS diagnosed on MRI, who also underwent a rs-fMRI sequence from August 2012 to October 2019. For each patient, 120 independent components extracted from the rs-fMRI data were independently classified into four categories (noise, resting state network, epileptic network, and unknown) by two radiologists who were blinded to the electroclinical data and morphological imaging. From these networks, each radiologist determined the probable EZ lateralization.
Results: There was a strong agreement (87%) between the EZ lateralization determined by rs-fMRI and the one determined by electroclinical data, imaging findings and post-operative outcomes. Interobserver agreement rate was almost perfect, with a K score of 0.84 (95% CI: 0,68; 1,00).
Conclusion: rs-fMRI is a non-invasive modality highly reliable and reproducible for localizing EZ in adults suffering from HS, including cases with discordant presurgical investigations. This modality could help in increasing the number of surgery candidates and avoiding invasive acts. Long-term objective is to incorporate this technique into routine pre-surgical evaluations as part of standard care.

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Complementary structural and functional abnormalities to localise epileptogenic tissue

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Purpose: When investigating suitability for epilepsy surgery, people with drug-refractory focal epilepsy may have intracranial EEG (iEEG) electrodes implanted to localise seizure onset. Diffusion-weighted magnetic resonance imaging (dMRI) may be acquired to identify key white matter tracts for surgical avoidance. Here, we investigate whether structural connectivity abnormalities, inferred from dMRI, may be used in conjunction with functional iEEG abnormalities to aid localisation of the epileptogenic zone (EZ), and improve surgical outcomes in epilepsy.
Method: We retrospectively investigated data from 43 patients with epilepsy who had surgery following iEEG. Twenty five patients (58%) were free from disabling seizures (ILAE 1 or 2) at one year. Interictal iEEG functional, and dMRI structural connectivity abnormalities were quantified by comparison to a normative map and healthy controls. First, we explored whether the resection of maximal abnormalities related to improved surgical outcomes. Second, we investigated whether concurrent use of both modalities improved the prediction of surgical outcome. Third, we suggest how connectivity abnormalities may be useful to inform the placement of iEEG electrodes as part of the pre-surgical evaluation using a patient case study.
Results: Seizure freedom was 15 times more likely in patients with resection of maximal connectivity and iEEG abnormalities (p=0.008). Both modalities separately distinguished patient outcome groups and when used simultaneously, a decision tree correctly separated 36 of 43 (84%) patients based on surgical outcome.
Conclusion: Structural dMRI may aid pre-surgical evaluations when EZ localisation is uncertain. Our approach suggests personalised iEEG implantations and resections which may lead to improved surgical outcomes.

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White matter abnormalities in children with mTORpathies and pharmacoresistant epilepsies

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Purpose: mTORpathies are a group of epileptic disorders associated with activation of mTOR pathways and pharmacoresistant epilepsies. Recent data show that maturation of oligodendroglia and production of myelin are impaired in mTOR disturbances [Gruber et al., Neuropathol Appl Neurobiol 2021;47:812-825). Our aim was to investigate individual white matter (WM) structural abnormalities in a group of children with mTORpathies.
Method: Eight individuals with pharmacoresistant focal epilepsies were included: 4 diagnosed with tuberous sclerosis complex (TSC) (2 males, mean age 9 years, range 8-13), 3 with epilepsy associated with surgically confirmed focal cortical dysplasia type IIB (FCD-IIB) (3 females, mean age 15 years, range 14-18), and one with epilepsy associated with pathogenic variant in the *NPRL3* gene without MRI signs of FCD (female, 7 years old). One patient had severe intellectual disability and two had borderline intellectual functioning. Voxel-based

morphometry analysis was performed using volumetric T1-weighted MRI sequences, with SPM12 software. The analysis was performed individually by comparing each individual participant with a group of age-matched healthy controls. Structural changes were classified into patterns (localized or diffuse; juxtacortical or subcortical) and anatomical distribution.
Results: Seven patients had diffuse and one (FCD-IIB) localized WM volume reduction. All individuals with TSC and two patients with FCD-IIB had diffuse juxtacortical and subcortical WM atrophy. One patient with FCD-IIB had localized juxtacortical and the patient with *NPRL3*-epilepsy had diffuse juxtacortical WM atrophy. The 3 patients with intellectual comorbidities (one with TSC and two with FCD-IIB) presented with the most prominent WM atrophy, including atrophy of the corpus callosum. No patient had WM atrophy in the cerebellum or brain stem.
Conclusion: Children and adolescents with mTORpathies have diffuse WM volume reduction. Intellectual comorbidities are associated with a more prominent pattern of WM abnormalities including the corpus callosum.

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Patterns of structural network abnormalities in children with developmental epileptic encephalopathies of genetic etiology

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Purpose: Developmental and epileptic encephalopathies (DEEs) are conditions in which epileptic seizures occur alongside cognitive or behavioral changes determined by the underlying cause and/or ictal or interictal discharges. Among the causes of DEEs, the genetic etiology is highlighted due to the increasing number of descriptions of involved genes. The objective of this study is to evaluate the patterns of structural alterations in white and gray matter (WM and GM) in the brains of children with DEEs of genetic etiology.
Method: Eleven patients with DEEs of genetic etiology were included in the study (6 females, mean age 9 years, range 1-18). Pathogenic or likely pathogenic variants were present in the following genes: *MTOR, KCNT1* (2)*, ASXC3, CLCN4* (2)*, SCN1A, MECP2, STXBP1, NRXN2* (2). Neuroimaging evaluation was performed using voxel-based morphometry analysis with volumetric T1-weighted MRI sequences through SPM8 software. Analysis was conducted individually by comparing each participant with a group of age-matched healthy controls. Structural changes were classified into patterns: localized or diffuse (for WM and GM); juxtacortical or subcortical (for WM); and the anatomical distribution.
Results: Cerebral atrophy was observed in all patients. WM atrophy predominated in a diffuse pattern, both juxtacortical and subcortical. GM atrophy predominated in localized regions, with the following anatomical distribution: temporal and occipital lobes, frontotemporal transition, left cuneus, and cerebellum. Two children with the same gene mutation and

similar phenotypes (*NRXN2* gene) exhibited a similar pattern of GM and WM atrophy, in the parietooccipital regions. Children with distinct variants and clinical phenotypes despite the same gene mutation (*KCNT1* and *CLCN4*) demonstrated distinct patterns of atrophy.
Conclusion: Children with DEEs of genetic etiology present a diffuse pattern of GM and WM atrophy, including areas associated with behavioral control and socioadaptive functions. The genetic variant may influence the network of brain abnormalities and consequently the clinical phenotype.

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A machine learning model for the detection of focal cortical dysplasia in FLAIR MRIs

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Purpose: Focal cortical dysplasia (FCD) is a leading cause of medication-resistant epilepsy but responds exceptionally well to seizure control through surgery. However, access to surgery is often restricted as FCD lesions are notoriously subtle and frequently missed during MRI manual review. Artificial intelligence has the potential to serve as a solution for lesion detection with precision and speed.
Method: FLAIR MRI sequences from 36 patients (ages 5 to 19 years) with MRI positive radiological findings for FCD from Arkansas Children's Hospital (Little Rock) EMU were used. The MRIs were annotated using 3D Slicer 5.5.5 for Windows (Fedorov et al., 2012) by an experienced epileptologist and a clinical neuroscience researcher. Discrepancies in the annotation were resolved via discussion between the annotators.
A semantic segmentation model was trained using the MRI/mask pairs. The machine learning (ML) model was built in Python 3.9 and the Tensorflow-GPU platform and trained using a dual GPU (NVIDIA Quadro RTX 8000) system. The ML architecture was a fully convolutional neural network (CNN) with layers of CNNs with increasing numbers of filters and max pooling to extract image features and then layered deconvolutional neural networks were used to generate the mask to be applied to the MRI image.
Results: The model was trained on 35 patient MRI FLAIR sequences for 500 epochs. The Dice coefficient had a maximum value of 0.88 and an Intersection over Union value of 0.86. The model was tested against the remaining patient MRI and achieved an accuracy of 90.2% concordance with ground truth.
Conclusion: We demonstrate the feasibility to automatically identify focal cortical dysplasia lesions by segmenting MRI images and highlighting suspected lesions using machine learning (ML) by extracting image features. This creates a more detailed MRI analysis than the currently used technique of visual manual review, promoting more timely and effective treatment.

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Prevalence, outcome and features of seizures in children with COVID–19 – single center experience

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Purpose: To evaluate the prevalence, outcome and features of seizures in children with COVID-19.
Method: Retrospective study includes all children with seizures associated with moderate or severe form of COVID-19 hospitalized in period from Octobar 2020-January 2022 in COVID Department at our hospital. The data about seizures were collected from observers (parents or physicians). Type of the seizures are classified according a new ILAE clasiffication 2017. Status epilepticus (SE) is defined according ILAE definition from 2015. EEG was done in all cases, and depending on indication neuroimaging was done. The outcome was assessed at the end of hospitalization.
Results: The seizures occurred in 24 of total number of 388 children with COVID-19. Mean age was 6 years (range 0.2 - 15). Focal and generalized seizures were observed in equal number of cases. In ten patients the seizures were associated with fever. Five children experienced SE (focal in 4, generalized in one). Seventeen patients had a new onset seizure while seven children with previous epilepsy had worsening of seizure control during COVID-19. Recurrent seizures during hospitalization occurred in six patients. EEG was done during the follow-up period (1-12 months) showing epileptiform discharges in 6/20 patients. Abnormal neuroimaging was in 4/17. The outcome was favorable in all cases except one case with brain tumor discovered during acute disease, and one case with encephalitis.
Conclusion: Prevalence of seizures in children with moderate or severe COVID-19 is 6.18%. Most of the cases (70.8%) have a new onset seizure, with low rate of seizure recurrence. SE occurred in 20% with good response to rescue medication. The outcome in children with seizure associated with COVID-19 is favorable.

Neuropsychology

1485

Diagnostic utility of quantitative electroencephalography (QEEG) for detecting periodic seizures and cycling periodic patterns

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Purpose: Periodic seizures (PS) are those recurrent electrographic seizures that occur at regular intervals. Previous studies used as a criterion the presence of at least three seizures per hour. Our study aims to describe their electroencephalographic (EEG) features to clarify their clinical and prognostic implications.
Method: This retrospective and descriptive study analyzed conventional EEG, continuous EEG monitoring (cEEG), and QEEG from patients diagnosed with status epilepticus (SE) between 2019 and 2023 at our institution. Clinical and neurophysiological data were reviewed. A maximum 30% variation in the periodic interval was set, applying exceptions in the case of subintrant seizures.
Results: The sample included 13 patients, 7 males and 6 females, with ages ranging from 17 to 89 years. Nine of 13 patients presented with motor symptoms, while four exhibited non-convulsive SE. Common causes of PS were not recognized. EEG abnormalities were focal in 11 of the 13 patients and none of them with temporal lobe involvement. Two patients with post-anoxic encephalopathy presented bilateral PS. Periodic lateralized discharges (PLD) were detected in 4/13 patients, and two of them showed a cycling periodic pattern. Seizure duration was less than 2 min in 11 patients, whereas the interval ranged between 16 s to 19 min. Three patients presented subintrant seizures. Eleven patients required a minimum of three anti-seizure medications, seven of them needed sedation and admission to the intensive care unit due to their super-refractory SE. Both patients with post-anoxic encephalopathy died during hospitalization.
Conclusion: Contrary to previous reports, our findings suggest that PC does not exclusively originate in posterior regions and may not have unfavourable prognostic implications. Compressed trends of QEEG facilitate the detection and interpretation of PS on EEG, which are likely to be underdiagnosed. Future investigations are required to elucidate the underlying mechanisms and optimize management strategies.

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Status epilepticus associated with the benzodiazepine withdrawal syndrome

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Purpose: Electroencephalography (EEG) plays a crucial role in diagnosing and managing status epilepticus associated with benzodiazepine withdrawal syndrome (SE-BZDw), particularly

with low clinical suspicion. The main objective of this study is to describe common EEG features that define a suggestive pattern.
Method: A retrospective and descriptive study analysed serial EEG recordings in patients diagnosed with SE-BZDw between 2008 and 2021, hospitalized in our institution. We obtained clinical, pharmacological, and neurophysiological data from 25 patients.
Results: The sample consisted of 13 females and 12 males, with 64% of the patients over 60 years old. All patients had a history of psychiatric disorders, with anxiety and depression as the most prevalent conditions (22/25). Other medications were usually associated with the prescription of benzodiazepine (BZD), predominantly antidepressants (19/25). Lorazepam was the BZD most frequently used (15/25). All cases had an abrupt cessation or indeterminate discontinuation of BZD treatment. While 68% of patients presented with motor seizures as their initial manifestation, the EEG revealed non-convulsive status epilepticus in 100% of cases, exceptionally with eyelid flutter or myoclonic jerks. An ictal-interictal continuum (IIC) pattern was found in the EEG with fluctuating rhythmic delta activity (RDA) in all patients and rhythmic theta activity (RTA) in eight patients, predominating on frontocentral regions and frequently bilateral. These RDA patterns often included spike and/or poly-spike waves (RDA+S), occasionally sharp/poly-spike wave complexes (SW, PSW), with evolving criteria in 15 patients. Fourteen patients were completely seizure-free in less than 36 hours. Administration of anti-seizure medication (ASM) and temporal reintroduction with BZD, was required in all cases. Eighteen patients needed ≤ 2 ASD. The mortality during hospitalization was 0%.
Conclusion: EEG is an indispensable diagnosis tool in the SE-BZDw, showing common characteristics that define a typical EEG pattern. Further prospective studies are required to validate these findings.

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Epi-Space – cognitive and psychosocial consequences of epilepsy in young adults

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Purpose: Epilepsy is a neurological disorder, that besides seizures, is characterized by cognitive and psychosocial symptoms that may have detrimental impact on patients' subjective wellbeing, their ability to complete education and finding and maintaining a job. However, in a clinical setting, these underlying complications of the disease are not systematically addressed and often underreported by patients. The objective of the present study was to address and assess these issues by establishing an interdisciplinary treatment program for young adults with epilepsy.
Method: Epi-Space was implemented from 2021-23 at the Department of Neurology, Aarhus

University Hospital, Denmark and included a total of 48 persons (65 % females) with epilepsy aged 18-30 years randomly selected from the Epilepsy Clinic.
The subjects underwent a thorough neuropsychological evaluation including standardized, validated cognitive tests (e.g., subtest from the Wechsler Adult Intelligence Scale and Wechsler Memory Scale) targeting implicated neuroanatomical areas and functions. The patient's cognitive profile was used in subsequent psychosocial counseling establishing collaboration with relevant parties e.g., school, municipality, or workplace.
Results: In total 42 out of 48 patients (88 %) completed the Epi-Space program. Neuropsychological assessment indicated cognitive difficulties within domains of executive functions (100 %), attention and working memory (31 %), and learning and episodic memory (24 %). Among the 42 patients, 20 patients (48 %) showed impairment within a single cognitive domain, while 21 (50%) showed deficits within two or more domains. At inclusion, 83% reported high levels of mental fatigue. Qualitative responses upon completing the program suggested enhanced psychological well-being, symptom-insight, and improved mastering of epilepsy.
Conclusion: Cognitive dysfunction and psychosocial challenges are common among young adults with epilepsy, even when patients don't report symptoms. Early identification and management of these consequences of epilepsy through interdisciplinary treatment is essential to improve individual mastering of epilepsy and enabling patient-centered collaboration across sectors.

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Oral language assessment in adults with aphasic epileptic status: a systematic review

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Purpose: Aphasic epileptic status in adults is difficult to diagnose (Marques et al, 2018) because it is frequently associated with symptoms as altered consciousness (Chung et al, 2002). There is little literature on assessment tests specific to epileptic language disorders in adults (Dutta et al., 2018) compared to tests of other cognitive dimensions which have received much more attention (Dutta et al., 2020). As a result, the consequences of epilepsy on language are greatly underestimated (Allaire, 2017). This review aims therefore to identify standardized tests specific to the assessment of oral language in epileptic adults and evaluate their psychometric properties.
Method: The literature search carried out in PsycINFO, PubMed and Scopus was : (epilepsy OR seizure) AND (assessment OR test OR evaluation) AND (language OR anomia OR lexical access OR comprehension OR production OR syntax OR fluency OR aphasia).
Results: 3'853 articles were selected and only 10 were included in the synthesis. There is an over-representation of naming tests, mainly the *Boston naming test* (Goodglass et al,

1983) which assesses lexical access in oral production. The minority of linguistic cognitive domains reviewed (oral comprehension; oral production & phonological short-term memory, oral production & executive functions, are semantic system) are respectively assessed by the *Token Test* (De Renzi & Vignolo, 1983) & the *Russian Aphasia Test* (Dragoy et al, 2016) & the *Western Aphasia Battery* (Kertesz, 1982), the *Word & verbal Fluency Tests* (Horn, 1983; Novelli et al., 1986; Tombaugh, 1999) & the *Pyramids and Palm Trees* (Howard and Patterson, 1992).
Conclusion: To date, there is no battery to assess specifically and completely language disorders in aphasic epileptic adults. The tests reviewed have questionable psychometric properties for assessing oral language in aphasic epileptic adults, since they were specifically developed to assess aphasia in neurodegenerative diseases (Alzheimer) and/or classic post-stroke aphasia in adult & older patients.

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Neurodevelopment outcome in Pyridoxine-dependent epilepsy from Sfax-Tunisia

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Purpose: Pyridoxine-dependent epilepsy (PDE) is a treatable neonatal epileptic encephalopathy with different patterns of long-term epilepsy evolution. Little is known about the long-term neurodevelopmental outcome.
Here we report the neurodevelopmental state of a cohort of PDE from Sfax (Tunisia).
Method: This is a longitudinal study of 14 patients with PDE confirmed genetically linked to the same pathogenic variant (c.1364T> C) of the ALDH7A1 gene. These patients are followed at the neonatology department during the neonatal period and after discharge at the child neurology department of Sfax University Hospital, over a 13-years period. All patients had a neurological examination and multidisciplinary assessment during the follow-up, particularly for oral and written language assessment, gross and fine motor skills, and neuropsychology evaluations with intellectual quotient measures.
Results: The mean age was 7 years 5 months [2 years 6 months – 13 years 7 months] with a sex ratio of 0.93. All patients except one are seizures free since the neonatal period except one during febrile illness. Brain MRI made in 65% showed diffuse white matter signal abnormalities and morphological abnormalities of the corpus callosum in 88%, diffuse brain atrophy in 55%, and posterior fossa abnormalities in 55%. Neurologic evaluation was normal in 18%. There were gross and fine motor disorders in 73% in favor of the diagnosis of developmental coordination disorders (DCD). One child (9%) had severe hypotonia with global motor and cognitive delay. Development of oral language was delayed in 62 % and normal in 38%. The neuropsychological assessment done in 58% showed a normal level in 37% and an intellectual disability in 63% (mild in 25%, severe in 38%).

Conclusion: Despite the early therapeutic management with control of epileptic seizures, the long-term evolution of PDE is of lower quality with a cognitive deficit and motor skills disorders responsible for academic difficulties.

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Mood influences acquisition, but not delayed recall or retention, on word list learning in epilepsy

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Purpose: A common referral question in neuropsychology is whether cognitive concerns might be due to mood. While it is well documented that subjective memory complaints are associated with low mood less is known about how mood influences objective memory performance. Given the frequency of depression in epilepsy it is important to know whether mood influences objective memory performance. Here we test the hypothesis that low mood negatively impacts objective memory scores, using data acquired in the Australian Epilepsy Project (AEP; https://epilepsyproject.org.au/).
Method: 282 adults (M_{age}=36.6, SD_{age}=12.8; 135 Male; 69 diagnosed with a First Unprovoked Seizure, 96 with a New Diagnosis of Epilepsy, and 117 with Drug Resistant Focal Epilepsy) recruited to the AEP completed the Rey Auditory Verbal Learning Test (RAVLT), the WAIS-II FSIQ-2, and the Neurological Disorders Depression Inventory for Epilepsy (NDDIE). The influence of mood on memory measures was analysed by comparing ANCOVA models, with IQ, RAVLT version, sex, age, diagnostic category and NDDIE score as independent variables.
Results: Learning (total words recalled across learning trials) was negatively associated with mood symptomatology. Learning was dependent upon IQ, RAVLT version and sex ($p<.01$); addition of NDDIE scores to the model significantly improved fit ($p<.001$).
Delayed recall and loss of words across delay were *not* dependent on mood symptomatology. Delayed recall was dependent upon IQ, RAVLT version and sex ($p<.01$). The number of words lost was dependent upon referral category and sex ($p<.05$). The addition of NDDIE scores to the above models did *not* significantly improve fit ($p>.05$).
Conclusion: Low mood reduces the amount of information acquired on a word list learning task but does not influence the delayed recall or retention of information that has been acquired. Thus, delayed recall and loss measures can be interpreted free of potential confounds from depressive symptomatology.

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Cognitive difficulties are evident at epilepsy diagnosis: evidence from the first 100 participants in the Australian epilepsy project

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Purpose: Research on the neuropsychology of epilepsy is primarily focused on those with chronic and pharmacoresistant epilepsy. Fewer studies have focussed on the newly diagnosed. Here we analyse neuropsychological data from the first 100 cases of the pilot Australian Epilepsy Project (AEP; https://epilepsyproject.org.au/) with a particular focus on comparing new diagnosis and pharmacoresistant focal epilepsy groups. We hypothesised that cognitive deficits would be present at diagnosis, and greater among those with pharmacoresistant focal epilepsy.
Method: Of the first 104 adults (M_{age}=35.3, SD_{age}=11.7; 49% Male, 50% Female) recruited to the pilot AEP, 25 (24%) were newly diagnosed and 46 (44.2%) had pharmacoresistant focal epilepsy. Pilot AEP participants completed traditional, examiner-administered neuropsychological measures via Zoom and five subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB).
Results: Participants in both the new diagnosis and pharmacoresistant focal epilepsy groups had reduced performances (relative to normative samples) on tasks of processing speed, complex attention/executive function, confrontation naming, and verbal learning and memory (all *p*'s < .001). Performance tended to be lower in the pharmacoresistant group, significantly so with regard to confrontation naming. Further, those in the pharmacoresistant focal epilepsy group had poorer performances on the CANTAB paired-associate learning task, purported to measure visual learning and memory, compared to the new diagnosis group and the normative sample. Examiner ratings indicated data collected using the CANTAB was more likely to be invalid because of *'distraction'*, *'misunderstood instructions'*, and *'refusal'*. Qualitatively, participants reported frustration with the CANTAB tasks.
Conclusion: Cognitive deficits are apparent at epilepsy diagnosis, with trends towards greater deficits in chronic epilepsy. Examiner-facilitated teleneuropsychology, in comparison to automated computer testing, elicits higher quality data and results in a better participant experience.

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Effect of endocannabinoids on cognitive functions in patients with treatment-resistant epilepsy

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Purpose: To assess the cognitive status and quality of life of adult patients with drug-resistant focal epilepsy before and after adjuvant treatment with cannabidiol (CBD).
Method: Open observational prospective cohort study. We included 55 patients with focal drug-resistant epilepsy, with functional levels of writing and reading comprehension. All patients started cannabidiol treatment with pure CBD oil formula, dose 250 mg/day (mean: 4.1 mg/kg/day), titration progressively up to 20 mg/kg/day. Patients were evaluated using a standardized domain-specific protocol (language, attention, memory, executive functions) before treatment and 6 months post-treatment. Quality of life was assessed using QOLIE-10. Student's t-test for related samples was used for statistical analysis using SPSS.
Results: 55 patients were included: 11 did not complete the study (9 dropped out, 2 were excluded). 44 patients were analyzed: mean age: 34,7 (SD 10) 19-60 years, 74% female, mean IQ was 83 (SD 15). The mean time epilepsy duration was 20 years (SD: 13). Seizure frequency: 38 patients (87%) reduced more than 50%.We found statistically significant changes in memory tasks ($p<0.00$): the Rey's Auditory Verbal Checklist and in the Rey Complex Figure test, in immediate and delayed recall tasks, and in the Trail Making Test B. Mean QOLIE-10 total score improved from enrollment (24,73 ± 6,98) to follow-up (19,26 ± 7,91; $p = 0.001$).
Conclusion: The evaluation post CBD treatment showed an improvement in memory and attention tasks, which we can attribute to the decrease in seizure frequency and the improvement in quality of life. This could significantly favor sustained attention, a necessary condition for the immediate retrieval in memory tasks, as well as the improvement in alternating attention. Further analysis is needed to observe the maintenance of these results, and to replicate it with a larger number of patients.

Neurostimulation

1617

Intracortical mechanisms of after-discharges elicited by intracranial 50 Hz stimulation of epileptic patients

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Purpose: Rhythmic stimulation-induced discharges, known as after-discharges (AD), have long been correlated with epileptogenic processes. Nevertheless, the latent neuronal processes, as well as its exact relationship with the epileptogenic zone (EZ), are still poorly understood.

Our goal was to delineate cortical domain-specific characteristics of ADs derived from intracranial macro- and microelectrode recordings.
Method: Our study examines the data of 14 drug-resistant epileptic patients undergoing presurgical evaluation with subdural grid electrodes, presenting prominent ADs in the course of a 50 Hz stimulation protocol. Simultaneously, laminar multielectrode arrays (LME) were also implanted in the hypothesized EZ. ADs were visually identified on the macroelectrode recordings of all patients. Six patients with LMEs placed near an AD-presenting electrode (at max. 2 cm distance), were selected for further analysis.
Results: We have examined both macro- and microelectrode recordings of 36 AD-series containing stimulation epochs, with overall 551 AD events. ADs detected on macroelectrode recordings proved to be very localised, only LMEs located in proximity (<0.5 cm) were able to register visible discharges. We have demonstrated that ADs contain prominent beta, gamma and high frequency components, emerging first in upper-middle layers (supragranular domain). While beta and gamma components peak in the superficial region, high frequencies achieve their maxima in lower layers. Nevertheless, the frequency pattern underlying individual events changes over the course of a series and is also dependent on distance from AD focus. Current-source density analysis revealed a marked sink in the infragranular domain, in case of LME recordings closest to the AD foci. There was a decrease in multiunit activity (MUA) following stimulation, which primarily engaged upper-middle layers, while AD peaks were accompanied by prominent MUA, encompassing all LME channels.
Conclusion: In sum, ADs primarily appear in the supragranular domain, but also engage lower layers. Additionally, ADs are associated with MUA peaks, however preceded by post-stimulation inhibition.

Paediatric Epileptology

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"Hidden" midline spikes in childhood epilepsies

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Purpose: In children, midline central and centro parietal spike are usually "hidden" amongst the sleep architecture especially in between the large vertex waves and are sometimes missed when EEG is reviewed only in bipolar montage. This is especially true when they occur exclusively and predominantly in the midline channels.

Objective: To determine the frequency of isolated midline centroparietal spikes in various childhood epilepsies.
Method: EEG record of children 2-12 years from Jan 2020 to Jan 2023 were reviewed both in bipolar and average montage. EEGs of children with midline spikes that were found most predominantly with maximum amplitude in midline centro parietal electrodes (CZ/PZ) with or without diffusion of field to adjoining parasagittal electrodes (C3/P3/C4/P4) were selected and the clinical and imaging data of these children were analyzed.
Results: Among total of 1580 EEGs reviewed, only 28 EEGs satisfied criteria. 25 of them had these spikes exclusively in a sleep record and 3 of them had these on awake and sleep record. None of these spikes were detected in an exclusive awake EEG record.
Out of 28, twenty five(89%) of these children had self-limited focal epilepsies mostly SeLEAS. Four of them had Developmental/Epileptic encephalopathy with spike- wave activation in sleep and three had focal epilepsies due to structural causes.
Previous EEGs were taken in 15 of them out of which these spikes were not reported in seven.
Conclusion: Hidden" midline spikes in childhood epilepsies can easily be missed if EEG is reviewed only in bipolar longitudinal montage and sleep record is not obtained. Their amplitude is seen maximum in the midline channels and they usually have a spike wave index of more than 30%. They are more conspicuously present in average montage and high suspicion is required to detect them and differentiate from normal sleep architecture. They are found most commonly in self-limited focal epilepsies of childhood.

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Safety and efficacy of intravenous lacosamide for acute seizures/status epilepticus in critically ill children

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Purpose: Acute seizures/status epilepticus are common in critically ill children. The aim of the study is to evaluate the effectiveness and safety of intravenous lacosamide in critically ill children with acute seizures/status epilepticus.
Method: This retrospective study included children who received intravenous lacosamide from October 2017 to September 2022 in the pediatric intensive care unit of a medical center. Previous healthy group with new lacosamide initiation and patients with epilepsy (with or without continuation of outpatient oral lacosamide) were enrolled. The loading dose of lacosamide was 10 mg/kg and the maintenance dose was 12 mg/kg daily. Efficacy was defined as cessation of seizures within 72 hours of administering lacosamide. Adverse effects were defined by predefined criteria, and most were evaluated during the first 7 days.
Results: We identified 67 children with intravenous lacosamide administration, including 42 boys (62.7%) and 25 girls (37.3%). Their mean age was 7.20±5.66 years. Among them, 30

(44.8%) had acute seizures, and 37 (55.2%) had status epilepticus. The seizure types were focal onset (34, 50.7%), generalized onset (27, 40.3%), and mixed type (6, 9.0%). In previous healthy group, cessation of acute seizures (n=9) after lacosamide in first two line occurred in 100.0%, and cessation of status epilepticus (n=23) after lacosamide in first to fourth-line occurred in 100, 80.0, 50.0, and 50.0%, respectively. In patients with epilepsy, cessation of acute seizures (n=21) after lacosamide in first to second-line occurred in 71.4 and 42.9%, and cessation of status epilepticus (n=14) after lacosamide in first to third-line occurred in 80.0, 75.0, and 100.0%, respectively. 18 (26.9%) patient experienced bradycardia and 1 (1.5%) patient experienced a rash.
Conclusion: Intravenous lacosamide was efficacious for acute seizures/status epilepticus in first to second line in critically ill children. Further study is warranted to evaluate the effectiveness of earlier lacosamide use in these population.

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A human cortical assembloid model of Dravet Syndrome (DS)

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Purpose: Animal models have been instrumental in advancing our understanding of DS pathogenesis and as preclinical models to test advanced gene therapies. However, important genomic differences in *SCN1A* regulation between rodents and humans and influences of the genetic background may hinder our ability to effectively translate preclinical findings in rodents onto the clinic.
Method: Patient-derived somatic cells can now be converted into human iPSCs, capable of differentiating into a variety of cellular lineages. Leveraging this, the generation of stem-cell derived 3D cell cultures – known as organoids – allows to model brain structures in remarkably complex ways. Cortical assembloids are generated from the fusion of a cortical and a subpallial organoid, which allows the generation of both excitatory and inhibitory cortical neurons and recapitulates the tangential migration of cortical interneurons from the subpallium into the cortex, as it occurs *in vivo*.
Results: Importantly, we have observed Nav1.1 expression at later stages of development in this model. Therefore, we generated iPSC lines from three Dravet patients and corrected two of them using CRISPR-based genome editing. We have established a protocol to record LFP (local field potentials) in intact assembloids. By recording evoked epileptiform activity in mature assembloids using this protocol, we have observed for the first time a clear epileptic phenotype in DS assembloids.
Conclusion: Our human DS cortical assembloids could be pivotal to better understand disease pathogenesis in a human context and to improve preclinical testing of novel advanced thera-

py strategies.

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Preventing epilepsy using vigabatrin in infants with tuberous sclerosis complex (PREVeNT Trial)

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Purpose: To test the hypothesis that early vigabatrin treatment in Tuberous Sclerosis Complex (TSC) infants improves neurocognitive outcome at 24 months of age.
Method: Phase IIb multicenter randomized double-blind placebo-controlled trial of vigabatrin at first epileptiform EEG vs. vigabatrin at seizure onset in infants with TSC. Primary outcome: Bayley-III cognitive assessment score at 24 months. Secondary outcomes: prevalence of drug resistant epilepsy, additional developmental outcomes, and safety of vigabatrin.
Results: Of eighty-four infants enrolled, 12 were screen failures, four went straight to open label vigabatrin, and 12 were not randomized (normal EEG throughout). 56 were randomized to early vigabatrin (n=29) or placebo (n=27). 19 of 27 in the placebo arm transitioned to open-label vigabatrin with a median delay of 44 days after randomization. Bayley-III cognitive scaled scores at 24 months were similar for participants randomized to vigabatrin or placebo. Additionally, no significant differences were found between groups in overall epilepsy incidence and drug resistant epilepsy at 24 months, time to first seizure after randomization, and secondary developmental outcomes.
Incidence of infantile spasms was lower and time to spasms after randomization was later in the vigabatrin group. Adverse events were similar across groups.
Conclusion: Preventative treatment with vigabatrin based on EEG epileptiform activity prior to seizure onset does not improve neurocognitive outcome at 24 months in TSC children; does not delay onset or lower the incidence of focal seizures and drug resistant epilepsy at 24

months. Preventative vigabatrin was associated with later time to onset and lower incidence of infantile spasms.

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Analysis of seizures in children with anti-glutamic acid decarboxylase antibodies related encephalitis/encephalopathy

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Purpose: The aim of this study was to evaluate whether serum anti-glutamic acid decarboxylase (GAD) antibody titers were associated with the presentation of seizures in children with encephalitis/encephalopathy.
Method: In this single-center retrospective cohort study, we enrolled hospitalized children who had encephalitis and/or encephalopathy with positive anti-GAD antibodies in serum and/or cerebrospinal fluid from February 2010 to October 2021.
Results: Among the 37 enrolled children, seizures were common and occurred in 30 (81.1%) patients. Status epilepticus was presented in 11 (29.7%) patients, and 4 of them were diagnosed with febrile infection-related epilepsy syndrome (FIRES). Seventeen patients were allocated to the high-titer group (serum concentration $\geq$ 100 U/mL) and 20 patients to the low-titer group. There were no significant differences in the rate of seizure presentation or EEG abnormalities between the two groups. The level of titers was not associated with severity or outcomes. Serial titers of serum anti-GAD antibodies were obtained in four patients. Two of them had seizures, and one was diagnosed with FIRES.
Conclusion: Seizures were common in children with anti-GAD antibody-positive encephalitis/encephalopathy. Status epilepticus was presented in 11 (29.7%) of the patients. The level of the titer was not significantly correlated with the rate of seizure presentation, the severity or outcome.

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Perinatal stroke results in a significant lifetime risk of epilepsy

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Purpose: To examine the risk of epilepsy following perinatal stroke.
Method: Data is part of a Danish cohort study examining the morbidity following perinatal stroke. Data was extracted from the nationwide Danish Medical Birth Registry and National Patient Registry, including all liveborn children born past GA >33+6 from 1997 to 2018. We included 1.327.686 individuals. Follow-up was from date of birth until epilepsy, death, emigration, or the 31st of December 2018, whichever occurred first. The maximum follow-up time was 22 years. We compared the cumulative incidence/risk (CIN) of epilepsy in children with and without perinatal stroke, considering death a competing risk.
Results: We identified 825 (0.06%) children diagnosed with perinatal stroke, resulting in an overall prevalence of 6.2 per 10.000 individuals (ranging from 4.5–9.1 per annum). Overall mortality was markedly higher in children with perinatal stroke (18% vs. 0.3%), with two-thirds dying in the neonatal period.
In total, 61% of the cases also had neonatal seizures versus 0.1% of the controls. The overall CIN of epilepsy in children with perinatal stroke was 21.5% (95% CI 18.2–24.7%) compared to 1.3 (1.27–1.33%) in children without ($p<0.001$). Strikingly, the cumulative risk of epilepsy was higher in children with neonatal seizures, but no diagnosis of perinatal stroke, compared to children with stroke, but no neonatal seizures (19.9% (17.9–21.9) vs. 12.4% (8.3–16.4)). Nevertheless, the cumulative risk peaked in children with both perinatal stroke and seizures (27.5% (22.8–32.1)).
Conclusion: Children with a perinatal stroke have a high risk of death, especially in the neonatal period. Children who survive have a substantial risk of epilepsy, being more than 16 times higher than children without stroke. Notably, neonatal seizures are important when considering the following risk of epilepsy in all children, but especially in children diagnosed with a perinatal stroke.

1507

A **child with a rare pathogenic variant c.678dup, p.(Leu227iLefster4) in the in exon 7 of UBEZA gene at Angelman syndrome and epilepsy**

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Purpose: Angelman syndrome is rare and belongs to the group of genetic imprinting disorders where pathogenic mutations in the active gene are responsible for the disease, while pathogenic mutations in the inactive gene do not cause the disease. It's caused by problems with a gene located on chromosome 15 called the ubiquitin protein ligase E3A (UBE3A) gene. Some of pediatric patient don't have a family history of the disease. Genetics examination is very important.
Method: Targeted massively parallel sequencing of exogenous protein-coding genes in the human genome (WES) using second-generation sequencing (NGS) technology and bioinformatic processing of genes associated with patient condition. PCR amplification of exon 7 of the UBEZA gene and direct sequencing with the BigDye Terminator Sequencing kit according to the Sanger method and analysis on the AB-PRISM 3500 automatic analyzer.
Results: We present to you a 2 and a half year old female child with seizures which are difficult to control and recur in clusters, alternating with periods without attacks. Due to suspicion of epilepsy sent for genetic diagnosis. The presence of a pathogenic variant c.678dup, p.(Leu227iLefster4) in the in exon 7 of UBEZA gene in heterozygous form was proven. there is a change in the reading frame (frameshift), i.e. replacement of the amino acid leucine at position 227 with the amino acid isoleucine and termination of the protein after 4 amino acids. This variant has not been published in the literature so far. Family studies showed that the c678dup variant in the UBEZA gene was not present in the child's parents. Additional analysis confirmed the biological connection of the parents with the child. These findings confirm that the pathogenic c678dup variant in the child arose de novo. Anticonvulsant therapy was prescribed and ketonic diet.
Conclusion: Early diagnosis of Angelman syndrome and appropriate therapy enables a better quality of life for children.

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Long-term outcomes of children with infantile epileptic spasms syndrome in South Korea

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Purpose: Infantile epileptic spasms syndrome (IESS) is characterized by epileptic spasm and chaotic electroencephalographic abnormalities, frequently associated with developmental regression or stagnation. Children with IESS frequently evolve to other epilepsy types or drug-resistant epilepsy (DRE), and they have poor neurodevelopmental outcome. We aimed to demonstrate the long-term seizure and neurodevelopmental outcomes of infantile epileptic spasm syndrome.
Method: We retrospectively reviewed the medical records of patients with IESS from five tertiary centers in South Korea. Patients with the onset of spasm before the age < 2 years who had follow-up data at least 2 years were included in this study. Demographics, treatment regimes, seizure and neurodevelopmental outcomes were collected.
Results: A total of 435 patients with IESS were included. The median duration from the first to the last hospital visit was 99 months. The median onset age of spasms was 8.6 months. About 19% of cohort had epilepsy before the onset of spasms. Most of them (92% of entire cohort) had vigabatrin, and 31% of cohort had steroid to control spasms. Of 435 patients, 99 (23%) had diet therapy, and 19 (4%) had epilepsy surgery. At the last visit, of 422 patients, 30% were considered as drug-resistant epilepsy, 22% had non-disabling seizures with anti-seizure medications (ASMs), and 26% achieved seizure control with ASMs. About 22% of entire cohort were seizure free without taking ASMs. Of 431 patients, 97 (23%) of them evolved to Lennox-Gastaut syndrome. About 90% of overall cohort had intellectual disability at the last visit.
Conclusion: Children with IESS has poor seizure and neurodevelopmental outcomes. Approximately, 78% of them required long-term ASMs to control seizures and 30% were considered as DRE. In addition, 90% of them had intellectual disability and required special education.

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Refractory epilepsy, macrocephaly with hydrocephalus, leukodystrophy, severe hiponatremia- neonatal presentation of Alexander disease with novel *GFAP* missense heterozygous variant NM_002055.5: c.1187C>T

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Purpose: The authors present neonatal form of Alexander disease with a rapid course of severe drug-resistant epilepsy and novel first-described variant of Alexander disease.
Method: Exome sequencing was performed on the proband's DNA extracted from blood using Twist Human Core Exome 2.0 + Comp Spike-in + Twist mtDNA Panel (Twist Bioscience, South San Francisco, CA, USA). Enriched library was paired-end sequenced (2x100 bp) on

NovaSeq 6000 (Illumina, San Diego, CA, USA). Data analysis and variants' prioritization was performed using in-house bioinformatic pipeline.
Results: In the first weeks of life, the child presented with increasing apathy, severe-limited activity and lack of eye tracking. Family and gestational history were non-relevant. At the age of 5 weeks, due to increased intracranial pressure ventriculoperitoneal shunt was implemented. MR revealed changes in basal ganglia, midbrain, corticospinal tracts, progressing in 1-week follow-up to generalization and contrast-enhanced lesions. Focal-onset motor seizures with secondarily generalization lead to introduction of phenobarbital. Due to its inefficacy, antiepileptic treatment was modified with levetiracetam, then temporarily phenytoin was used, then clobazam and carbamazepine. The glucose concentration in cerebrospinal fluid was significantly reduced and ketogenic diet was introduced. Lysosomal storage disorders, organic acidurias, fatty acid oxidation defects were excluded. The epilepsy panel by NGS showed no abnormalities, GLUT1 deficiency was excluded. At the age of 4 months, the head circumference was 43 cm with lack of eye and verbal contact, limited spontaneous activity. In EEG abnormal SBA type with localized, lateralized and generalized lesions. A follow-up brain MRI showed abnormal diffuse increased signal of white matter, deep structures, cerebellum and medulla oblongata. In the proband novel *GFAP* missense heterozygous variant NM_002055.5: c.1187C>T, p.(Thr396Ile) was considered as disease-causing.
Conclusion: The presented patient is the second described worldwide representative of the severe neonatal form of Alexander disease, but first with a novel pathogenic *GFAP* variant.

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The first global consensus guidelines for the diagnosis, care and treatment of SCN8A-related disorder

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Purpose: To develop guidelines to facilitate earlier diagnosis of the diverse phenotypes of SCN8A-associated disorders, develop clear treatment protocols based on data, reduce inequity in care and support the best possible outcomes for all those living with SCN8A-related disorders.
Method: We established a Core Panel with 12 clinicians and 5 families familiar with SCN8A-related disorders, and divided these into three workgroups: 1. Diagnosis and phenotypes, 2. Treatments, 3. Comorbidities and prognosis. Each group completed a structured literature review and developed questions for the first round of the Delphi survey. A larger international group of 29 clinicians and 13 families, spanning 5 continents served as the expert panel for the modified Delphi process. Three rounds of survey questions were completed to gain increased consensus or clarification on key points. Strong consensus required 80% or more agreement; moderate 67-79%.
Results: We established consensus on five distinct phenotypes. Consensus was strongest for typical features and recommended therapy for the Severe DEE phenotype with more limited consensus for the four other phenotypes - Moderate DEE, SeL(F)IE, Neurodevelopmental Disorders (NDD) with and without seizures. There was strong consensus that in those with Severe DEE, more than half of the time present with intense challenges with fine and gross motor skills, speech, intellectual disability, sleep disturbances, GI issues and hypotonia while those with NDD most often present with speech delays and intellectual disabilities. There was also high consensus that those with gain-of-function variants, sodium channel blockers should be considered first-line therapies and levetiracetam avoided. Major areas of uncertainty remain and will require further investigation.
Conclusion: This important process confirmed 5 distinct SCN8A phenotypes and provided strong consensus on the typical presentation and recommended treatment for the Severe DEE phenotype and some features of other phenotypes, which will aid in more targeted diagnosis, treatment and care for those with SCN8A-related disorders.

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Clinical and electrophysiological synergistic effects of highly purified cannabidiol and fenfluramine on three paediatric patients affected by Dravet Syndrome

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Purpose: Dravet syndrome (DS) is a rare Developmental and Epileptic Encephalopathy (DEE) characterized by onset during infancy, drug-resistant epilepsy and several comorbidities such as behavioural, cognitive, motor and sleep disorders. The pharmacological treatment of seizures in DS radically changed with the introduction of highly purified Cannabidiol (CBD) and Fenfluramine (FEN). No data is available on the effect of the combination of these new options in the treatment of seizures in DS. We aim to report the synergistic effect of CBD and FEN on the electroclinical course of patients with DS.
Method: We collected clinical data, video-EEG recordings and results of Griffith developmental scales of patients with DS treated with an association of CBD and FEN for a minimum of 3 months.
Results: We enrolled three patients (2 males, mean age 8 years). All patients presented generalized febrile tonic-clonic seizures at onset (mean age at onset 6 months), evolving in status epilepticus in two cases. First General Quotient (GQ) was normal for all.
Within 3 years-old all patients developed myoclonic absences. One patient presented with myoclono-atonic seizures, one massive myoclonus. Two patients had photosensitive epilepsy, with diffused polyspike-and-wave at eye closure and self-inducing behaviour.
All patients presented developmental delay at last evaluation (mean GQ 49,03 – mean age 6.8 years) and reduced attention span. One patient has oppositive behaviour.
Patients were previously treated with Valproate, Stiripentol, Clobazam, Ethosuximide, Topiramate, and Clonazepam. After the initiation of CBD and FEN patients had a reduction in spontaneous and self-induced myoclonic seizures, with the persistence of polyspike-and-wave at eye closure in photosensitive patients. All patients had an increased the attention span and improved behaviour.
Conclusion: The combination of FEN and CBD has had a significant effect on the neurological condition in patients with DS, by reducing the seizure burden and possibly having a cognitive modulating effect.

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Case report: cannabidiol in migrating focal epilepsy with SNC1A mutation

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Purpose: The purpose is to discuss whether add-on cannabidiol therapy determined a variation in seizure frequency.
Method: 3-year-old female, presenting with severe drug-resistant epileptic encephalopathy-classified as migrating focal epilepsy- with neonatal onset in SNC1A de novo mutation, developmental delay, microcephaly, movement disorder.
She experienced her first seizure at 39 hours of life and has never been seizure-free. Her sei-

zures are polymorphic in type, with major episodes being characterized by diffuse hypertonia with apnoea and ocular deviation, followed by clonias and minor episodes being atypical absences with ocular deviation. Her EEG recording shows spikes and spike-and-waves, predominant on the left anterior region. These anomalies are more frequent and diffuse during drowsiness; during sleep we observe continuous diffuse symmetrical spike-and-waves, more evident on the left anterior region, with no evident physiological sleep waveforms.
A number of anti-crises drugs have been tried, with the current therapy being lacosamide, valproate, clobazam and cannabidiol. In the past clonazepam, levetiracetam, phenytoin, midazolam, ketamine during status epilepticus and cycles of ACTH have been administered. Periciazine was added for irritability.
Results: Cannabidiol has been administered for 14 months to this day, at the dosage of 10 mg/kg. When prescribed, in Italy it was off-label due to age, since the patient was less than 2 years old. Before cannabidiol, she presented 1-2 major crises per month. After reaching the final dosage, the toddler presented 2 major motor seizures, at 10 and 14 months of treatment, both during an infectious event (pneumonia) that required hospitalization. No other major episodes have been observed. Brief absences still persist unaltered.
Conclusion: Cannabidiol as an odd-on therapy was effective in reducing major seizures in early onset epileptic encephalopathy with migrating focal seizures associated with SCN1A gene mutation, although these can still manifest during severe infections.

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A family with misleading migraine attacks diagnosed as occipital lobe epilepsy

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Purpose: Ictal elementary features during occipital lobe seizures often overlaps with visual aura of a migraine attack. Differential diagnosis seems challenging in the pediatric population due to the labor in collecting data relating to clinical phenomenology in children and the possible coexistence of both condition.
Method: We describe a case of a female adolescent whose migraine attacks was confused with a focal onset occipital lobe seizure.
Results: A 17-year-old female with a family history of migraine and epilepsy came to our observation for acute decreased visual acuity. The adolescent reported monocular fuzzy and strange moving objects for few minutes, which disappeared giving rise to blurred vision and headache during two hours. Ophthalmological examination _during the attack_ found a visual acuity limited to 2/10 on the right and a discreet narrowing of the visual field. Ocular Tomography, visual evoked potential and eletroretinogram were normal. At interrogation, the patient also complained from intermittent hemi-cranial headache accompanied by nausea,

photophobia, and sonophobia. These episodes were drug resistant and lasted for hours. After alternative diagnoses were ruled out through extensive investigations (normal Brain CT scan and electroencephalogram), our patient was diagnosed with Retinal Migraine. The history of her mother and brother treated for epilepsy respectively since the ages of 26 years and 4 years was reviewed. In both, the the diagnosis of epilepsy was doubtful because continuation of attacks until adulthood is an unlikely finding in the setting of self-limited epilepsy.
Conclusion: A detailed clinical recording on the timing, duration and characteristics of neurological attacks including visual impairment, headache as well as vegetative features can help avoiding diagnosis mistakes and subsequent adequate therapeutic indication.

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Assessing the effectiveness of functional hemispherectomies conducted in a public children's hospital in Panama

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Purpose: To examine the effectiveness of functional hemispherectomy surgeries conducted in Panama between 2005 and 2023
Method: Functional hemispherectomies were performed in children meeting the criteria for drug-resistant epilepsy at the Jose Renan Esquivel Children's Hospital in Panama City, Panama, between January 2005 and May 2023. Prior to the surgeries, patients' medical histories were taken, and 1.5 Tesla MRI scanners were used to capture images with and without contrast. Video-EEG monitoring was used to record at least 2 characterizations of paroxysmal activity. Surgeries were performed through a collaboration involving doctors and hospital staff from the United States, Argentina, and Panama. Surgical techniques performed included lateral hemispherectomy, with disconnection of the insula, temporal mesial structures, corpus callosum, parieto-occipital connections and basal frontal. Patients were followed-up for over two years to assess prognosis. The Engel Epilepsy Surgery Outcome Scale was used to classify outcomes.
Results: Twenty-four surgeries were conducted in patients with a mean age of 9.5 years-old (Range: 3.5-16 years-old). 87.5% of patients were followed-up for over a year. Post-surgery complications included bleeding (8.3%), infections (8.3%) and post-operative hydrocephalus (4.0%). Two years after surgery, 16.0% of patients had an Engel class IIB outcome. The remaining 83.0% of patients had an Engel class IA or IB outcome.
Conclusion: The functional hemispherectomy surgeries performed in Panama over the last 18 years have led to successful outcomes, with most patients being free of disabling seizures

after two-years of follow-up post-surgery. Panama is a middle-income country, with a broad population pyramid for those under 19 years-of-age and increasing rates of epilepsy among children. The establishment of an epilepsy surgery program for functional hemispherectomies involving international assistance has improved the quality of life of numerous children and their families. Establishment of similar programs could be helpful for countries of similar income-level.

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A rare case of pathogenic variant of c.784G>T, p.(Asp262Tyr) in exon 9 of the STXBP1 gene with clinical manifestation of developmental and epileptic encephalopathy 4

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Purpose: Developmental and epileptic encephalopathy 4 is a neurological disorder characterized by the appearance of tonic seizures in early childhood, usually in the first months of life. clinically manifested by impaired psychomotor development with poor head control, limited or no ability to walk, spastic quadriplegia and weak or absent speech. The purpose of this study is to use early genetic examination for diagnosis
Method: Targeted massively parallel sequencing of exogenous protein-coding genes in the human genome (WES) using second-generation sequencing (NGS) technology and bioinformatic processing of genes associated with patient condition.
Results: We present to you a 4 and a half year old with generalized tonic-clonic seizures. The EEG finding is characterized by focal epileptic activity, generalized spike and slow waves. In the genetic analysis showed the presence of a pathogenic variant of c.784G>T, p.(Asp262Tyr) in exon 9 of the STXBP1 gene in a heterozygous form. It is a missense change that causes the amino acid aspartic acid at position 262 to be replaced by the amino acid tyrosine. The examination of the parents did not show the presence of the variant c.784G> T, indicating that it arose de novo. Pathogenic changes in the STXBP1 gene are associated with developmental and epileptic encephalopathy 4 , which is inherited in an autosomal dominant manner. The biological connection of the parents with the child was confirmed by a complementary analysis
Conclusion: Early diagnosis of developmental and epileptic encephalopathy 4 and introduction of new therapy will enable a better quality of life for children

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Acetazolamide for developmental and/or epileptic encephalopathy with spike-wave activation in sleep (D/EE-SWAS). Experience Dr Exequiel González Cortes Hospital, Chile

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Purpose: To describe effect of acetazolamide in patients with D/EE-SWAS.
Method: Fourteen D/EE-SWAS patients treated with acetazolamide were described. Acetazolamide initial and maintenance doses were defined. Response criteria were complete SWAS-improvement or reduction to <10% and clinical improvement . First, second and third EEG were obtained 1-6 months(EEG-1), 6-12 months(EEG-2) and 12-24 months(EEG-3), after acetazolamide started. Adverse drug reactions were under surveillance.
Results: In 3/14 patients etiology was structural (perinatal sequelae) and in 11/14 no-structural (genetic syndrome, SeLECTS and other non-structural genetic epilepsy).
In 9/14 acetazolamide was used as add-on therapy and in 5/14 it was used instead of previous drugs.
In EEG-1, response was observed in 11/14 patients but in 3/14 there was no-response and the dose of acetazolamide increased.
To this date, EEG-2 was obtained in 12 out of the 14 patients (9/11 patients who responded in EEG-1 and in 3/3 non-responsive patients).
In 8/11 patients who responded in EEG-1, they maintained responsive in EEG-2. A relapse was observed in one previously EEG-1 responsive patient (required dose increase) and in 3/3 remained unresponsive despite dose increase.
Preliminary results of EEG-3 are still under development.
Etiology of responsive patients was structural as well as non-structural. The non-responsive patients all had non-structural causes (other non-structural genetic epilepsy).
Adverse reactions were reported in 3/14 patients (headache and decreased appetite).
Conclusion: Response was observed in approximately 70% cases, despite etiology . The majority o who responded in EEG-1 maintained response in EEG-2. On the other hand, patients who did not respond in EEG-1 continued unresponsive in EEG-2 despite dose increase. These cases had preexisting developmental delay and non-structural genetic epilepsy; we suppose an underlying genetic mutation associated with greater severity. .
Although further follow-up time is needed for the series, acetazolamide could be effective and safe for treatment of D/EE-SWAS when sulthiame is not readily available.

Psychiatry

Difficulties with sleep and motor coordination in secondary school-aged children with epilepsy: a case control study

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Purpose: The primary aim was to compare the prevalence of difficulties with sleep and motor coordination in children with 'active' epilepsy (11-15 years) (n=60) and a healthy control group (n=49). The secondary aim was to explore relationships between sleep, motor coordination and quality of life (QOL) in the children with 'active' epilepsy.
Method: Children with 'active' epilepsy, controls and caregivers completed a measure of child sleep (Insomnia Severity Index and Child Sleep Habits Questionnaire respectively). Caregivers also completed a measure of child motor coordination – Developmental Coordination Disorder-Questionnaire (DCD-Q). The children completed a measure of QOL - Pediatric Quality of Life Inventory. Comparisons between the epilepsy and control group were undertaken using chi-square analysis and independent t-tests. The relationship between sleep, motor coordination and QOL were explored using correlational analysis. Alpha level was $p<0.05$ and effect sizes are reported using Cohen's d.
Results: The epilepsy and control group were well matched on age, gender, and socioeconomic status. Children with epilepsy had more sleep difficulties than controls on self- ($p= 0.003$; $d = 0.581$) and caregiver report ($p<0.001$; $d=1.230$). Children with epilepsy were significantly more likely to be at-risk for DCD than controls (45% vs 12%; $p<0.001$). Caregivers of children with epilepsy reported that their child had more motor coordination problems on the three DCD-Q subscales: Control during movement ($p<0.001$; $d= 0.746$), Fine motor/handwriting ($p<0.001$; $d = 0.658$) and General coordination ($p<0.001$; $d=0.947$). In the epilepsy group there was a significant negative correlation between QOL and sleep ($p<0.001$; $r = 0.502$) and QOL and motor coordination ($p<0.001$; $r =0.592$). Children with sleep difficulties and coordination difficulties had worse QOL.
Conclusion: Secondary school-age children with epilepsy should be screened for sleep and motor coordination difficulties. Future research should focus on interventions to support children with epilepsy to reduce the impact of these difficulties on QOL.

1537

The physician's role in reducing health disparities for persons with epilepsy and intellectual disability: "it's not just epilepsy…you really have to take a deeper dive."

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Purpose: Epilepsy affects approximately 25% of people with intellectual disability (ID). Despite the high prevalence, evidence of health disparity exists in health access and health outcomes for this population. This qualitative study aimed to explore the views of physicians supporting individuals with ID on why they believe such health disparities occur and how best they may be addressed.
Method: Semi-structured interviews were carried out in May 2023 with six physicians, located in four countries, who specialise in the care of persons with ID who have epilepsy. Specialties included: general and paediatric neurology, psychiatry, and general medicine. Interviews sought views on prognostic expectations, experiences of disparities in epilepsy care, and suggestions for advocacy interventions. Transcribed interviews were analysed using reflexive thematic analysis.
Results: Four core themes were identified. (1) *'I don't know what I'm doing'* reflected participants' descriptions of a nervousness by colleagues when treating epilepsy in persons with ID. (2) *'Taking a deeper dive'* illustrated the harmful effects of accepting "common dogma" such as concerns that "drugs cause problems" or a resignation that "[there's] nothing you can do." (3) *'Not the strongest players'* captured the additional challenges faced by persons with ID in accessing appropriate epilepsy care, and the importance of having somebody to advocate on their behalf. (4) *'Teach me'* highlighted the importance of physicians acknowledging the patient with ID, and their carer, as experts by experience who can support the physician with treatment plans.
Conclusion: Patients with epilepsy and ID comprise one of the most disadvantaged patient cohorts with epilepsy. The expectations, attitudes and actions of physicians are key in addressing health disparities in this patient group. Education and training, taking time to learn how to communicate in different ways, and regular reflection on personal assumptions and biases are important contributors in addressing the inequalities experienced by this population.

Social Issues

1450

Development and validation of epilepsy life skills guidelines for primary school learners and teachers in Limpopo and Mpumalanga Provinces

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Purpose: The study aimed to develop life skills education guidelines for primary school learners of Limpopo and Mpumalanga provinces in South Africa to educate them about epilepsy and reduce stigma and discrimination towards people with epilepsy.
Method: The guidelines were developed following the World Health Organization (WHO) guideline development guide, which included the formulation of PICO (Population, Intervention, Comparison, Outcome) questions, conducting a systematic review of the literature, and using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) to develop evidence-based recommendations.
Results: The recommendations that informed the guideline development were that epilepsy life skills education should be included in primary school curricula to improve understanding, attitudes, and skills related to epilepsy. These programs should be tailored to the needs of primary school learners and cover topics such as seizure recognition, management, medication, and coping strategies. Collaboration between healthcare providers, educators, and policymakers is crucial to developing culturally appropriate and evidence-based programs. Teachers and healthcare providers should also receive training on how to support students with epilepsy.
Conclusion: The resulting guidelines provide clear and concise guidance on epilepsy life skills education for primary school learners, caregivers, and teachers. The guidelines are expected to improve the quality of epilepsy life skills education and contribute to the overall well-being and inclusion of learners with epilepsy in Mpumalanga and Limpopo Provinces, South Africa.

1481

Implementing intersectoral global action plan for epilepsy care in China

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Purpose: To implement the Intersectoral Global Action Plan for epilepsy and neurological disorders approved by the World Health Assembly 2022.
Method: We proposed a strategic plan for China focusing on epilepsy care by strengthening current national governance for epilepsy management and embracing novel approaches.
Results: The strategic plan is guided by 6 principles, including
1) people-centered primary health care and universal health coverage:
2) comprehensive care for epilepsy throughout life-span;
3) evidence-based policies and best practices;
4) intersectoral actions;
5) empowering and involving people with epilepsy (PWE) and their carers;

6) gender, equity, and human rights.
The relevant government departments organize and implement propaganda work centered on reducing stigma and discrimination to epilepsy, and establishing or improving epilepsy-related legislation, especially laws for education, employment, driving, and marital rights.
Conclusion: By 2031, specific goals would be achieved in China:
1) 90% of the public are aware of the correct knowledge of epilepsy;
2) 80% of provinces and cities have comprehensive tertiary epilepsy centers that can manage refractory epilepsy, and 80% of the counties have primary epilepsy centers with epilepsy specialist diagnosis and treatment capabilities;
3) 80% of community hospitals have 1 doctor who can engage in epilepsy diagnosis and treatment, and 3 or more commonly used anti-seizure medications (ASMs);
4) 80% of PWE receive standardized diagnosis and treatment, and 70% of seizures are effectively controlled;
5) 80% of regions have ASMs covered by medical insurance;
6) at least 2 relevant policies regarding the rights and interests of PWE are implemented;
7) a national public welfare epilepsy care center and a rescue fund are established;
8) epilepsy is integrated into the management of public health framework, and a set of core epilepsy indicator data is regularly collected through the national health information system every three years.

1490

Improving epilepsy education in lower middle income countries' schools: reducing misconceptions about epilepsy to improve epilepsy awareness in Pakistan and India

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Purpose: Nearly 1/6th and 1/10th of the global burden of epilepsy lies in India (Amudhan et al. Ann Indian Acad Neurol 2015;10:263–277) and Pakistan (Siddiqui et al. PJNS 2015; 10:47-49), respectively. This cross-sectional study evaluated baseline epilepsy knowledge and identified knowledge gaps through interventions teaching seizure first aid in Pakistani and Indian schools.
Method: In-person educational sessions were conducted by local volunteers in five schools in Pakistan (n=540; ages 10–15) and five in India (n=459; ages 10-15). Two flyers, a seizure action plan and an epilepsy fact sheet were distributed in English and local languages. Pre-and post-surveys were administered with open-ended and multiple-choice questions that measured educational outcomes and beliefs about epilepsy. McNemar's and chi-squared tests were used as appropriate for data analysis.
Results: The belief attributing epilepsy to supernatural causes significantly decreased from

51.9% to 10.9% in India (p<0.001) and from 47.2% to 17.5% in Pakistan (p<0.05) after intervention. Belief that epilepsy was contagious also reduced from 46.1% to 5.6% in India (p<0.001) and from 30.2% to 7.5% in Pakistan (p<0.05). Knowledge on proper seizure first-aid increased from 46.2% to 94.7% in India (p<0.001) and from 62.1% to 87.2% in Pakistan (p<0.05). Long-term epilepsy management knowledge increased from 36.9% to 84.9% in India (p<0.001) and from 23.3% to 75.0% in Pakistan (p<0.05).
Conclusion: Initial high rates of misconceptions about epilepsy in school children were recorded in both countries but significantly reduced after intervention. Findings highlight the value of targeted early-intervention school programs to address knowledge gaps and stigmas. Refresher sessions in schools are suggested to promote knowledge retention and reduce long-term negative effects of stigmas, including social isolation, hindered psychosocial growth, and school drop-out rates.

1514
Access to justice and realization of the rights of people with epilepsy

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Purpose: Purpose of the research is access to justice and realization of the rights of people with epilepsy. There are 60 000 people living with epilepsy in Finland and 50 million people in worldwide. People with epilepsy have a lot of problems with realization of legal rights and access to justice. According to the WHO (2022), although the social effects vary from country to country, the stigma and discrimination that surround epilepsy worldwide are often more difficult to overcome than the epileptic seizures themselves. There has been discussion in the research literature about legal status and legal problems of people with epilepsy. Long time in history people with epilepsy couldn't get married and it is still difficult in some countries. People with epilepsy have legal problems in many areas of life like education, employment, insurance, driving, and typically they meet discrimination.
Method: Quantitative survey & qualitative interviews. In the end of year 2022 our research team made a survey of realization of the rights for the people with epilepsy (n=237). In the year 2023 we will make also interviews.
Results: According to the preliminary results people with epilepsy have the most problems with healthcare, mistreatment and working life. There are also family problems, problems with housing and consumer problems. Epilepsy and seizures, stigma, discrimination, legal problems, and quality of life of people with epilepsy are connected to each other.
Conclusion: More information and communication about epilepsy is needed in society. The work of patient organizations plays a major role in this work.

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Overload, absenteeism, and presenteeism among caregivers of people with epilepsy

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Purpose: Introduction: Epilepsy is a common neurological disease with social, occupational, economic, and psychological repercussions for the patient and their family members.
Purpose: Identify indirect costs in epilepsy by overload, depression, absenteeism, and presenteeism among caregivers of people with Epilepsy through an online survey.
Method: An online survey was conducted among caregivers of people with epilepsy in Mexico. Sociodemographic variables were collected, as well as data on depression, overload, absenteeism, and presenteeism, using the Zarit, PHQ9, WPAI:GH and SPS-6 scales.
Results: Preliminary Results: In April 2023, 124 caregivers were surveyed online, of which 110 (88.7%) were women, and 65 (52.4%) had only elementary education. The majority were parents of the individuals with epilepsy (76.6%). Sixty (48.4%) experienced significant overload, but only 10 (8.1%) had severe depression. Two individuals (1.6%) received compensation for their caregiving role.
Sixty-five (52.41%) were salaried workers, dedicating an average of 7.41 + 3.5 hours per day to work, and reported an approximate annual income of 94,500 MXN (48,750-200,000) [4990 €] . The majority reported low work performance (53.8%), and the percentages of absenteeism were 11.5% for time lost at work, 9.35% for impairment during work, and 29.1% for general work disability.
Conclusion: In our sample, the presence of significant overload was very common, along with low work performance and general work disability among the family members and/or caregivers of people with epilepsy.
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Telemedicine as a path to bridging inequities in patients with epilepsy

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Purpose: Access to epilepsy specialist care is not uniform in the US with prominent gaps in rural areas. Reasons for non-attendance to epilepsy visits may help recognize access hurdles faced by patients. This study was undertaken to better understand the factors contributing to clinic absenteeism in epilepsy and how they may be influenced by telemedicine.
Method: Determinants of social health were collected for all adult patients scheduled in epilepsy clinic, either as an in-person or telemedicine appointment at University of Kentucky between July 2021 till December 2022. The primary outcome measure was attendance or absence at the appointment. Logistic regression modeling was used to identify factors leading to absenteeism at visits. In a subgroup analysis of the telemedicine visits, predictive modeling was conducted to recognize attributes that drive attendance.
Results: We included 3025 patient encounters from 1640 unique patients with a comparable number of in-person and telemedicine visits. The absentee rate was significantly higher for in-person visits (32%) compared with tele-visits (20%) ($p<0.001$). A logistic regression model identified six determinants of absenteeism, including prior missed appointments, Medicaid or Medicare as payors, no significant others, lower mean annual income, and minority race.
A prediction analysis for absenteeism at tele-visits (1382) showed individuals with Medicare/Medicaid, no significant others, and a tendency of no-showing were likely to miss appointments.
Conclusion: This study highlights that telemedicine is effective at improving attendance, overcoming socioeconomic hurdles, and widening access to epilepsy care. Disposal of specialist care improved among racial and ethnic minorities with telemedicine. Our findings show that the ability to utilize tele-care is strongly contingent on the insurance coverage available to the patient and emphasize the necessity of including telecare in insurance plans to ensure uniform access to high-quality epilepsy care, irrespective of socioeconomic status.

1583

Epilepsy in Zambia documentary

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Purpose: To bringing to the fore challenges faced by people with epilepsy, urging health authorities to revisit their policies on epilepsy care and inform about the ten-year Intersectoral Global Action Plan (IGAP) on Epilepsy and that WHO Member States are expected to implement the action plan. It was also hoped that first-hand information from persons with epilep-

sy describing the challenges, experiences and their successes would help the general public to change their attitude towards people with epilepsy, thus reducing the stigma and discrimination cases. Not to forget the effect on the care givers, a mother would give her views on the care for a person with epilepsy.
Method: Interviews with:
u The WHO Country Representative;
u IBE Africa Region - Secretary
u National Epilepsy Coordinator under MOH
u A neurologist (Pediatrician);
u Traditional Healer
u Traditional Leader; and
u Two youths - life story on epilepsy
Each participant had a role to play to strengthen the resolve to raise awareness, dispel myths and implement the IGAP.
Results: - The documentary conveyed through an interview with one youth, a teacher by profession, a message that the community should not allow youths' experience of epilepsy to define their lives, to realise that epilepsy is not a hindrance to progress, thus taking advantage of the seizure free moments to be productive in life.
- A clear message that caregivers should take their children to the hospital or health facility for correct diagnosis and treatment gave way to increased number of consultation at the Epilepsy Centre.
- Improved supply of anti-epilepsy medication in public health facilities,
Conclusion: The documentary was recorded in simple, uncomplicated terms and easy to follow with emphasis on the fulfillment of the IGAP goals and to help the health authorities, leaders and the community at large to understand epilepsy, thus reducing stigma and discrimination.

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Exploring community knowledge, attitudes, and perceptions of epilepsy in South Africa: implications for reducing stigma and improving care

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Purpose: This study aims to explore community knowledge, attitudes, and perceptions of epilepsy in the Limpopo and Mpumalanga provinces of South Africa to identify the challenges faced by people living with epilepsy (PLWE) in these communities.
Method: A qualitative exploratory-descriptive design was employed, using semi-structured interviews and focus group discussions with community members. Purposive sampling ensured

diverse participants across age groups, genders, and cultural backgrounds. Thematic analysis was conducted to identify common themes and patterns in the data.
Results: The findings indicate limited knowledge and understanding of epilepsy among community members and negative attitudes and perceptions towards PLWE. Community members viewed epilepsy as a brain disorder causing physical symptoms such as falling, shivering, and foaming at the mouth. Concerns were raised regarding PLWE's ability to perform certain jobs safely. However, positive attitudes were also identified, recognizing that PLWE can live normal lives and advocating for their support and inclusion. Some community members believed epilepsy could be cured, particularly through traditional medicine.
Conclusion: This study highlights the need for targeted interventions to address knowledge gaps, change negative attitudes, and reduce the stigma associated with epilepsy. Improving community awareness and understanding of epilepsy can contribute to better social integration and improved quality of life for PLWE. The findings of this study can inform the development of interventions that empower PLWE and their families, enhance access to healthcare and social services, and promote a more inclusive society.

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Foregone family employment in pediatric epilepsy patients

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Purpose: Costs of care in pediatric epilepsy are known to be considerable but remain incompletely quantified. Family economic status has been shown to impact health outcomes in children with special health care needs. With updated United States census survey data, we examine foregone family employment (FFE) because of a child's health condition in families affected by pediatric epilepsy.
Method: We conducted a secondary analysis from National Survey of Children's Health with updated data from the years 2020 and 2021. Respondents with children with epilepsy with employed adult family caregivers at the beginning of the survey period were included. The definition of FFE was any family member who reduced employment hours, took a leave of absence from work, or stopped work because of their child's health condition. Child, caregiver, and household characteristics were compared by reported status of FFE.
Results: 541 family respondents reported a child with epilepsy in the household during the survey time. 13 records were excluded due to missing values. 26% (95%CI 22%-29%) of previously employed families with children with epilepsy in their household experienced foregone

family employment. Multivariate analysis found that FFE correlated with higher severity of pediatric epilepsy, child's female gender, more time spent arranging healthcare per week, and increasing hours of family-provided home medical care.
Conclusion: One in four US families with children with epilepsy report foregone family employment. FFE is only part of a larger financial impact that has yet to be completely quantified. We highlight this area of socioeconomic burden of pediatric epilepsy to families as a call to action for further research as well as development of programs to address these gaps that can impact the health of these children and their communities overall.

1640

Celebrating epilepsy day: how it improves awareness and fights the stigma of epilepsy

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Purpose: This research focuses on Epilepsy Day, aiming to encompass all its aspects. Its purpose is to address various issues faced by individuals with epilepsy, which are often impacted by societal ignorance and economic challenges. We examine the progress of international and national efforts aimed at improving the lives of people with epilepsy. Additionally, we provide an overview of the celebration activities organized in selected African countries.
Method: We mainly reviewed journal articles to collect information and data for our study's objectives. The database solicited are PubMed, African and Middle East Epilepsy Journal, Scopus, Scholar Google. We sought social media too and the international health organizations pages and site. We also shared experiences of many associations in Africa and their founders on this matter.
Results: People living with epilepsy encounter numerous obstacles in various aspects of life, preventing them from leading a normal life. This triggered international health organizations to collaborate to address the challenges associated with epilepsy.
We conducted a comprehensive analysis of Epilepsy Day, including its historical background and the gradual progression towards establishing an International Day that unites the world for a noble cause: raising awareness about epilepsy and combating its stigmatization, with the ultimate goal of integrating people with epilepsy into society. We were particularly interested in the celebrations of Epilepsy Day in numerous African countries. Such as Morocco, Tunisia, Kenya, Uganda, DRC, Ethiopia, Cameroon, Rwanda, and The Gambia. In which, associations organize workshops, conferences, meetings under the lead of the Epilepsy Alliance Africa.
Conclusion: Epilepsy challenges necessitated the establishment of an Epilepsy Day to seek solutions and ultimately eradicate the issues or, at the very least, make progress towards that goal. The efforts of international health organizations in this regard must remain consistent, be more effective and expand awareness about epilepsy on a broader global scale.

Status Epilepticus

1525

Efficacy of the staged treatment approach in status epilepticus - an observational study SENSE

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Purpose: In epilepsy, the likelihood of becoming seizure-free decreases substantially with each unsuccessful treatment. To our knowledge, this has been little studied in status epilepticus (SE). We aimed to evaluate the proportion of SE cessation and functional outcome after successive treatment steps.
Method: We conducted a post-hoc analysis of a prospective, observational, multicenter cohort (SENSE), in which 1049 incident adult episodes were prospectively recorded at 9 European centers. We analyzed 996 episodes without coma-induction before the second treatment step. Rates of SE cessation, SE persistence, mortality (both in SE and after SE end) and favorable functional outcome at discharge (good outcome: mRS 0-2 or lack of worsening between admission and discharge) were evaluated after each treatment step.
Results: SE was successfully treated in 838 (84.1%) patients, 147 (14.8%) had a fatal outcome (36% of them while still in SE). Patients were treated with a median of three treatment steps (range 1-13) with 540 (54.2%) receiving more than two steps (refractory SE, RSE) and 95 (9.5%) more than five. SE was controlled after the first two steps in 45%, with additional 21% treated after the 3rd and 14% after the 4th step. Treatment sucess was 45% after the first two steps, 38% after the 3rd and 38-40% thereafter. Likelihood of SE cessation ($p<0.001$), survival

(p=0.003), and good functional outcome (p<0.001) significantly decreased between the first two treatment lines and the 3rd but remained relatively stable afterwards.
Conclusion: The likelihood of SE cessation significantly differed between the first two treatment steps and the 3rd, which clinically reflects the concept of RSE. However, unlike in chronic epilepsy, RSE remains treatable in around 30% of patients thereafter. Our results emphasized that SE cessation could be achieved even after prolonged RSE and failure of multiple treatments. This should warn clinicians against premature treatment cessation in selected RSE cases.

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ACTH secreting olfactory neuroblastoma in a patient with status epilepticus

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Purpose: Olfactory neuroblastoma (ONB) is a rare endocrine tumour arising from the olfactory bulb. The usual symptoms of ONB are nasal blockage and epistaxis. Reported neurological manifestations are headache and signs of local invasion.
Method: A 40-year-old lady, with a 2-month history of diabetes, hypertension and acute myocardial infarction presented with behavioural changes. She developed right focal motor convulsions with loss of awareness, which evolved into status epilepticus. Status-epilepticus was managed at the intensive care unit with 2 days of intravenous antiepileptic medications.
Results: She had monomorphic acne on upper-torso and resistant hypokalaemia(1.6mmol/L). High chromogranin-A(300.63ug/L), cortisol(2000nmol/L) and ACTH(38pg/mL) were detected. Imaging confirmed normal pituitary and enlarged adrenal glands. PET scan detected high FDG avid in the right-nasal-polyp. Biopsy confirmed ACTH secreting ONB with positive immunohistochemistry for the synaptophysin, chromogranin and ACTH. Grade-C tumour was penetrating the right cribriform plate with the enhancement of the adjacent dura of the frontal lobe. Even before the polyp removal all the metabolic abnormalities recovered and fits settled. But she had fear, anger, and intrusive thoughts. The normalization of serum cortisol implies the cyclical nature of Cushing syndrome with ONB. Background slowing of EEG persisted for 3-weeks with prominent slowing in the right side and temporal discharges. Anti-neuronal antibody panel and NMADR antibody were negative. The patient underwent complete surgical resection and is currently on two oral antiepileptics without further seizures.
Conclusion: Our patient didn't have any of the usual symptoms due to ONB. Seizures due to ONB is rare. Treatment of status epilepticus comprises managing the convulsion and treating the precipitating cause. Hypokalaemia is not a recognized cause of epilepsy. The mechanism of seizure manifestation could be due to local irritation or paraneoplastic.Achieving a seizure remission even before the lesionectomy, recent onset behavioural changes and electroencephalography findings in the right temporal area suggest a paraneoplastic aetiology.

1607

Longitudinal serum neurofilament light kinetics in post-anoxic encephalopathy

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Purpose: Studies have shown high serum neurofilament light (sNfL) concentrations predict poor outcome after cardiac arrest (CA), but data are limited to samples collected within 72 hours. We investigated longitudinal kinetics and time specific prognostic potential of sNfL up to 10 days after CA.
Method: We prospectively recruited all consecutive patients with post-anoxic encephalopathy due to CA admitted to Cardiocentro Ticino over the last 2 years. Serum samples were collected at admission and 1, 3, 5, 7 and 10 days after CA. sNfL concentrations were measured in duplicate with the NF-light assay. We analyzed EEG patterns associated with sNfL levels and extent of brain damage. Main outcome was mortality at discharge and 6 months after CA.
Results: We collected 252 samples from 62 patients, of which 28 (45.2%) died before hospital discharge and one 4 months after discharge. sNfL concentrations were positively associated with age (β=4.1 p=0.007) and days since CA (β=24.6, p<0.001). Differences in sNfL between survivors and non-survivors at discharge were subtle at admission (14.2 [8.6-21.9] vs 22.5 [14.2-46.9] pg/ml), but large at 24 hours (16.4 [10.2-293] vs 464.3 [151.8-1,658.2] pg/ml). When predicting mortality, the AUC for sNfL was above 0.95 from day 1 to 10, and highest on day 3 (AUC=0.99, 95%CI=0.98-1.00), with sNfL >444.7 and <114.6 pg/ml predicting mortality and survival with 100% specificity, respectively. Among patients with EEG (n=27), suppressed and/or generalized periodic discharges (GPD) patterns had higher sNfL than slow backgrounds (β=724.8, p<0.001).
Conclusion: We provide longitudinal kinetics of sNfL in post-anoxic encephalopathy up to 10 days after CA. sNfL measurements performed >72 hours after CA also have prognostic value. We provide time-specific cut-offs for death and survival, to be integrated and replicated in future studies of larger sample size. We confirmed that malignant EEG patterns reflect the extent of brain injury as measured by sNfL.

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Benzodiazepine-resistant status epilepticus among children in northern Nigeria

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Purpose: To determine the frequency of benzodiazepine-resistant (BR) among children with status epilepticus (SE) in northern Nigeria.
Method: Three paediatric emergency units (EPUs) in Kano, Nigeria adopted a status epilepticus (SE) protocol with benzodiazepines (midazolam or diazepam) as first line anti-seizure medicine (ASM) for SE. The childhood status epilepticus and epilepsy determinant of outcome (SEED) project includes teams of SE-trained nurses and EEG techs available 24/7, who ensured timely benzodiazepine administration upon SE diagnosis by a physician, using the ILAE operational SE definition. Electronic data were collected directly into REDCap© for children enrolled in SEED using android tablets with secure data uploaded directly to the Vanderbilt data coordinating center. Institutional ethics committee approvals were obtained.
Results: Between August 15, 2021 and May 31, 2023, of the 617 children actively seizing in SE who were administered benzodiazepines as the first drug in the SE protocol, 509 stopped seizing after the first dose of the benzodiazepine (82.5%). One hundred of the 108 children who continued seizing after a first dose of the benzodiazepine received a second benzodiazepine dose, and 68 of these 100 children (68%) stopped seizing, while 32 of these children were determined to be BR. The SE-associated short-term mortality among those who were BR was 46.9% (15/32), while the SE-associated short-term mortality among those who responded to benzodiazepines was 165/577 (28.6%).
Conclusion: Childhood SE in northern Nigeria is associated with high mortality and relatively low BR (32/609, 5.3%) compared to high-income countries where BR is up to 25%

Terminology and Classification

1609

The ENGenE App: development of an EpiCARE/ILAE educational tool on epilepsy nosology and genetic etiologies

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Purpose: To develop a simplified interactive decision-making process tool for trainees and non-experts caring for people with epilepsy that will enhance and stratify knowledge regarding the new syndromic classification with a special focus on genetic etiologies.
Method: A decisional algorithm was developed based on the fourty epilepsy syndromes included in the 4 Position Papers of ILAE Classification and Definition of Epilepsy syndromes developed by the ILAE Task Force on Nosology and Definitions (*Epilepsia*, 2022). The decisional trees included the mandatory, alert and exclusionary criteria for each syndrome, as defined in the papers. The trees were implemented as a web app using Typescript and the React framework.
Results: The user follows a step-by-step symptom-checker approach starting from a case's demographical characteristics, seizures' details, clinical and neurodevelopmental evaluation, EEG details, radiological information and other investigations. Based on the above information, the decisional algorithm gradually excludes syndromes with non-corresponding criteria resulting in a list of excluded, likely, unlikely/uncertain epileptic syndromes that could correspond to the clinical presentation of the case. For the "likely" syndromes, the App further provides information about the syndrome, its differential diagnosis, genetic information including (when applicable) a list of most frequent causative genes, transmission mode, genetic test(s) to be prioritized, possible targeted treatments etc. (information based on the nosology papers and further reviewed/updated by the authors). The tool was finalized following an in-person review meeting by a group of experts in epilepsy and genetics that were not implicated in its initial development. A two-stage validation procedure is ongoing. It will be accessible before September 2023 through a web-based application, hosted also on EpiCARE's webpage.
Conclusion: ENGenE App is an "intelligent" educational approach to the new classification of epileptic syndromes and their genetic etiologies, opting for early and appropriate diagnosis in all settings.

*Funded by EpiCARE CEF Telecom 2020 grant and ILAE.