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Epilepsy India



Newsletter of the Indian Epilepsy Association & Indian Epilepsy Society

New Definition for Epilepsy
International Epilepsy Day announced



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Dear All,
Greetings from Epilepsy India Editorial team.

ECON 2014, the joint Annual Conference of IEA and IES at Kolkata, was a resounding success. Dr. Arabinda Mukherjee has sent the highlights of this event to be published in this issue.

Briefly touching on the Presidential Oration delivered by Dr. Nadkarni and the Bajoria Oration delivered by Ms. Suchitra Narayan (who is President, IEA Kochi Chapter), both were of great practical value. Dr. Nadkarni, in her own inimitable simplistic style, gave an in-depth analytical approach to the role of AED monitoring in epilepsy management. She brought out an algorithm for the same to make it simple in day to day practice.

Ms. Suchitra, highlighted how epilepsy affects other domains, particularly in children. For the clinicians, obsessed with seizure control as the end all of epilepsy management, this talk should stimulate us to see epilepsy beyond seizures.

It was in 1960, that bone health problems associated with AED use were first reported. We should be alert about this, particularly in children, women and the elderly. Dr. Bindu Menon from Nellore, has given a scholarly article on Bone Metabolism and AED use in this issue.

Some random thoughts

Nature gives us a lot of insight into our health and disease states. Epilepsy is a disease of the brain (using

the term disease instead of disorder as per new ILAE definition) wherein excitation prevails over inhibition. The chief inhibitory neurotransmitter GABA (Gama Amino Butyric Acid) is really a metabolite of the chief excitatory transmitter Glutamate. Does it follow that more excitation, more glutamate, and hence more GABA, more inhibition and hence no seizures? Unfortunately no! The basic scientists have, over two decades, been working on single gene polymorphism which could explain up regulation of gene encoding for glutamate or down regulation of gene encoding GABA in persons with epilepsy. The Academia regulating medical education should lay more stress on basic sciences in medical graduate curriculum. At present, the attitude is one of forgetting the basics after clearing the exams.

The ILAE has come out with a new working definition of Epilepsy. Dr. Robert Fisher, Chair of the working group discusses the new definition and its significance for the readers of *Epilepsy India* (kind courtesy, the World Body) Dr. K.P. Vinayan, my Co-editor has given a brief editorial commentary on the new definition.

At last we have an International Epilepsy Day, the first is on 9th February 2015. Subsequently it will be observed on the second Monday of February every year. This was a long pending need as it will help co-ordinate awareness activities across the world and produce a major impact on spreading the message that we have to offer.

I hope we will get a lot of feedback from the readers on my random thoughts and on the applicability of the new working definition in our country. ■

International Epilepsy Day : Announcement

Posted by admin - July 7, 2014 - Activities, Featured News, Global Campaign Against Epilepsy, Joint Task Force, News, Press Releases Statements, Press Room, Uncategorized

The International Bureau for Epilepsy (IBE) and The International League Against Epilepsy (ILAE) are delighted to announce the creation of International Epilepsy Day.

This joint initiative of the IBE and the ILAE will be a major event celebrated across the globe in the 138 of countries in which IBE and ILAE are represented. With both IBE and ILAE in official working relations with the WHO, and with IBE in Special Consultative Status in the Economic and Social Council (ECOSOC) of the United Nations, this will make International Epilepsy Day the most prestigious epilepsy event in the world.

The first International Epilepsy Day will take place on Monday, 9th February 2015. Following on from this, the official day will be the second Monday of February each year. This world day for epilepsy will be a major step in improving epilepsy awareness in every region of the world, and will also highlight the urgent need for increased research into epilepsy.

Recognising regional diversity, IBE's members are grouped within seven regional structures following the WHO regional boundaries: Africa, Eastern Mediterranean, Europe, Latin America, North America, South East Asia and Western Pacific. IBE currently has 135 members in 104 countries. ILAE currently has 115 chapters in 127 countries.



New Operational Definition for Epilepsy and a Novel Approach from ILAE

Dr. Vinayan K.P.

Member, Pediatrics Commission, ILAE



ILAE has recently been in the process of modifying the definitions and classification of epilepsy keeping in tune with the improvements in understanding of the neurobiology and in the diagnostic techniques. In the last two decades, several taskforces worked on this project coming out with well thought out proposals for defining and classifying epilepsies. However, these proposals had very minimal impact on the practice of clinical epileptology globally.

Why was it so? We can attribute many reasons. The term epilepsy includes a wide spectrum of etiologically and neurobiologically dissimilar conditions, the common binding factor being the occurrence of clinical seizures. Provoked seizures were traditionally kept out of the ambit of the definition of epilepsy. The 2005 proposal from ILAE conceptually defined epilepsy based on the classical electroclinical approach as an enduring predisposition to have epileptic seizures. Each epileptic seizure was further defined as a clinical symptom/sign due to an abnormal, excessive and/or synchronous neuronal activity in the brain. However, there are no clear criteria to objectively measure this enduring predisposition in clinical practice.

The definition of epilepsy based on the occurrence of two unprovoked clinical seizures with at least an interval of 24 hours between them is considered as the most practical in any setting. However, such a purely clinical definition does not fully take into account the current understanding of clinical epileptology and may not follow the current practice patterns. The clinical diagnosis of epilepsy, most of the time, is aided by diagnostic investigations. EEG was always a clinically useful parameter in the electroclinical approach of epilepsies. The clinicians are now increasingly utilizing radiological and genetic investigations for an etiological diagnosis and also to predict the chance of seizure recurrence in specific situations. For example, the presence of a focal cortical dysplasia in imaging or a genetic anomaly like SCN1A mutation may indicate

a relatively high chance for seizure recurrence, even after the very first seizure. The new operational definition has tried to accommodate these clinical realities.

Any definition of epilepsy should be simple and be applicable in all clinical scenarios. It is a reality that epilepsy practices significantly differ across the geographic regions and also from primary to tertiary care centers in the same region. It is very difficult to draft a uniform definition applicable to all clinical care settings and at the same time maintain scientific accuracy. A rigorous definition incorporating all the advances in diagnostics may better reflect the current understanding about epilepsy. However, such a definition will not be clinically applicable in the rural primary care setting of a resource poor country and may not be useful to define the burden of epilepsy in such a community. The taskforce addresses this issue by providing multiple pathways for the clinical definition of epilepsy.

The new operational definition was formulated by a very novel, more democratic approach and it reflects the changing trends in medical science. It is not only a proposal prepared by a group of 'experts' after reviewing the available scientific data, based on consensus in a closed room. The initial draft proposal, prepared by the taskforce was put in public domain on the ILAE website. Comments and opinions were sought actively from all interested persons and the draft was modified after carefully considering these opinions. After approval by the board, the final manuscript was published in *Epilepsia*, following a blind peer review. An opinion poll is currently in progress on the *Epilepsia* website where any person with an active interest in epilepsy can comment on the acceptability of the proposed definitions in his practice.

The new operational definition is definitely a step forward and it tries to reflect the current practice of

epilepsy worldwide. There are several unresolved issues in the definition, especially the estimation of the probability of a second seizure after the first unprovoked seizure in many clinical settings and etiologies. Further focussed clinical research may hopefully be able to provide some of these missing links.

ILAE has requested all member chapters to disseminate this information amongst its members and discuss the applicability of the definitions in their

respective regions. The Editorial team at Epilepsy India feels it is very important to have a discussion on this topic and is planning to bring out a series of articles in the subsequent issues from the key opinion leaders of the epilepsy movement in our country.

In the following pages, you will find a summary of the salient features of the new definition by Dr Robert Fisher, chair of the working committee group, for the benefit of patients and caregivers.

Kavitha Shanbhag



Kavitha Shanbhag seen here receiving the very first NGO Challenge Award in the Communication and Outreach category from Digital Empowerment Foundation.

Kavitha Shanbhag is the Vice President of Indian Epilepsy Association (IEA), Bombay Chapter & elected Governing Council Member for the 2013-15 term. She is also the founder of ChildRaise Trust which works towards empowerment of special needs children & with a focus on disability issues.

www.childraise.com- a cross disability web-portal was launched on Dec 3rd 2001, on the occasion of the International Day for People with Disabilities (IDPwD). For over a decade, ChildRaise has been making use of Information & Communication Technologies (ICT). They soon introduced "ChildRaise Information Services-CRIS" under which a Resource Guide-Journey to Empowerment: a roadmap for Special Needs Children, a directory of rehabilitation services for parents, caregivers & professionals was published. In 2010, under CRIS, Child Raise launched DISHA -Disability Helpline & Action: a Toll Free Disability Helpline Tel No- 1800-22-1203, the last four digits representing Dec 3rd (IDPwD).

ChildRaise has successfully used various ICT tools like internet services, other internet based

tools such as social media networking sites besides other telecommunication means such as telephone, mobile phones to connect with beneficiaries to fulfill the organisation's mission of RAISE-Rehabilitation, Awareness, Information, Support & Education.

The 'eNGO Challenge' was initiated by Digital Empowerment Foundation (DEF) to recognise NGOs using ICTs for Impact. The Founder & Director of DEF Osama Manzar says that "There are more than 3.3 million NGOs in India according to the Govt. registration files. Yet, the amount of information & knowledge an NGO creates and documents never comes into universally accessible public domain. But considering internet is cheap, accessible, open and sharable, publishing is instant. Therefore, all NGOs should come online & help spread information sharing & digital literacy". With this vision, in year 2012 for the first time DEF partnered with Public Interest Registry, one of the top level domain managers of '.ORG.' to start the eNGO Challenge Award. They received about 167 nominations across 5 categories-1) Advocacy 2) Sustainable Development 3) Communication & Outreach 4) Social Commerce 5) Organizational Efficiency.

ChildRaise Trust is the recipient of the very first eNGO Challenge Award in the Communication & Outreach category. ChildRaise was selected for adopting innovative ICT approach & tools to reach out & publicize the activities and work with impact oriented outcomes for organisational efficiency and for stakeholders. While receiving the award, Kavitha Shanbhag, founder of ChildRaise Trust said, "We are very proud and humbled that our efforts in using ICT tools are being recognised. Using ICT has made a huge difference in our information dissemination strategy. It has strengthened our belief that Information is Power & it can change lives!!".

The 2014 Definition of Epilepsy :

A perspective for patients and caregivers

Robert S. Fisher

Department of Neurology & Neurological Sciences
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Seizures and epilepsy are not the same. An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. Translation: a seizure is an event and epilepsy is the disease involving recurrent unprovoked seizures.

The above definitions were created in a document generated by a task force of the International League Against Epilepsy (ILAE) in 2005. The definitions were conceptual, (theoretical) and not sufficiently detailed to indicate in individual cases whether a person did or did not have epilepsy. Therefore, the ILAE commissioned a second task force to develop a practical (operational) definition of epilepsy, designed for use by doctors and patients. The results of several years of deliberations on this issue have now been published (Fisher RS et al. A practical clinical definition of epilepsy, *Epilepsia* 2014; 55:475-482) and adopted as a position of the ILAE.

A commonly used definition of epilepsy heretofore has been two unprovoked seizures more than 24 hours apart. This definition has many positive features, but also a few limitations. This definition does not allow the possibility of “outgrowing” epilepsy. Inclusion of the word “provoked” seems to imply that people who have photosensitive seizures provoked by flashing lights or patterns do not have

epilepsy; whereas, most people think that they do. Some individuals who have had only one unprovoked seizure have other risk factors that make it very likely that they will have another seizure. Many clinicians consider and treat such individuals as though they have epilepsy after one seizure. Finally, some people can have what is called an epilepsy syndrome and these individuals should meet the definition for having epilepsy even after just one seizure. You should not have an epilepsy syndrome but not epilepsy. The new definition of epilepsy addresses each of these points.

A person is considered to have epilepsy if they meet any of the following conditions:

1. At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

In the definition, epilepsy is now called a disease, rather than a disorder. This was a decision of the Executive Committees of the ILAE and the International Bureau for Epilepsy. Even though epilepsy is a heterogeneous condition, (having several

causes) so are cancer or heart disease, and those are called diseases. The word “disease” better connotes the seriousness of epilepsy to the public.

Item 1 of the revised definition is the same as the old definition of epilepsy.

Item 2 allows a condition to be considered epilepsy after one seizure if there is a high risk of having another seizure. Often, the risk will not precisely be known and so the old definition will be employed, i.e., waiting for a second seizure before diagnosing epilepsy.

Item 3 refers to epilepsy syndromes such as benign epilepsy with central-temporal spikes, previously known as benign rolandic epilepsy, which is usually outgrown by age 16 and always by age 21. If a person is past the age of the syndrome, then epilepsy is resolved. If a person has been seizure-free for at least 10 years with the most recent 5 years off all anti-seizure medications, then their epilepsy also may be considered resolved. Being resolved does not guarantee that epilepsy will not return, but it means the chances are small and the person has a right to consider that she or he is free from epilepsy. This is a big potential benefit of the new definition.

What will change as the result of this new definition? Although revision of the definition has generated some controversy, it is likely that real-world changes will be fairly minor. Some people will be able to say their epilepsy is resolved. Others may encounter the problems and stigma of being told that they have epilepsy after one seizure in some circumstances, rather than after two seizures. The definition might stimulate research on how likely another seizure is after a first seizure in various clinical circumstances. Governments and regulatory agencies, people who do therapeutic trials for epilepsy, insurance companies and other third-party payers might have to adjust

some of their definitions. One reason changes will be small is that individuals with one seizure and a high risk for another are currently practically thought of as having epilepsy by many treating physicians. This process simply formalizes that thinking.

Making a diagnosis of epilepsy is not the same as deciding to treat. Some seizures are minor; some patients choose to avoid the side effects of medications. Treatment decisions will be individualized between a person with epilepsy and a physician. Sometimes, information is incomplete; for example, a possible seizure may not have been observed. In these conditions it can be impossible to confidently diagnose epilepsy using any definition. Clinicians will apply best judgment when faced with such incomplete information and often will wait for future developments.

This practical definition is designed for clinical use. Researchers, statistically-minded epidemiologists and other specialized groups may choose to use the older definition or a definition of their own devising. Doing so is perfectly allowable, so long as it is clear what definition is being used. In the process of developing the revised definition of epilepsy, consensus was reached by forging opinions of 19 co-authors of the publication, while accounting for criticisms by five anonymous journal reviewers and over 300 public commenters on the ILAE website. The revised definition is not perfect. It will become more useful over time as we gain better information on seizure recurrence risks. But for now, the new definition better reflects the way clinicians think about epilepsy.

Reference

Fisher R, Acevedo C, Arzimanoglou A et al, *Epilepsia* 55(4):475–482, 2014

Adapted from ILAE official website <http://www.ilae.org/Visitors/Centre/Definition-2014-Perspective.cfm>



The 15th Joint Annual conference of Indian Epilepsy Association and Indian Epilepsy Society was held in Kolkata on 31st January, 1st & 2nd February 2014 at the Taj Bengal.

The Pre conference workshop was held on 31st January and was attended by 250 participants. The theme was "Pediatric Epilepsy". In the pre lunch session, topics on "Paroxysmal Non epileptic disorders in children" were discussed. Post lunch topics included "Epileptic encephalopathies". Dr. F. Dimario (USA), Dr. Philippe Ryvlin (France), Dr. Ulrich Stephani (Germany), Dr. Deb Pal (UK), Dr. Rohit Das (USA), Dr. Vrajesh Udani (India), Dr. Manjari Tripathi (India)

and Dr. P. Satishchandra (India) presented their talks with case presentations which were well appreciated by the delegates and evoked good audience participation.

The main conference on 1st & 2nd February 2014, was attended by 460 delegates from all over India. The conference program included four orations, two symposia, award papers, platform and poster presentations. The West Bengal Medical Council awarded 8.3 hours CME credit for the conference.

The Presidential oration was delivered by Dr. V. V. Nadkarni, President IEA. The topic was "Antiepileptic drug monitoring - a level headed approach". The



Shobha Arjundas oration was delivered by Dr. S K Shankar. Dr. Ambar Chakravarty and Ms. Suchitra Narayan delivered the A D Sehgal and the H C Bajoria orations, respectively.

A new addition to Econ 2014 was the CPC. This was highly appreciated by all. Congratulations to Dr. Manjari Tripathi, Dr. M C Sharma, Dr. Joy Desai and Dr. Man Mohan Mehndiratta for their commendable contributions.

The excellent academic program was supplemented by social programs which included talks by people with epilepsy and care givers from different parts of India.

A stage drama organized by Dr. Goutam Ganguly drew applause from all including press and media.

The entertainment program on 31st January was performed by children of Manovikas Kendra, a school for mentally challenged children. They performed

on various percussion instruments. This unique program drew applause from the audience and touched everyone's heart.

Usha Uthup, a noted singer performed on 1st February.

The inauguration function was brief and the speakers addressed the issues on epilepsy. Ms. Chandrima Bhattacharya, MOS, Health & family welfare, Govt of West Bengal was Guest of honor and Sree Subrata Bakshi, Member of Parliament, was present as chief guest. Dr. Nirmal Maji, President WBMC, attended as special guest. The meeting was presided by Dr V V Nadkarni, President, IEA. Dr Arabinda Mukherjee, organizing chairman, read the welcome address, Dr Pravina Shah, President IES, addressed the gathering. Dr Man Mohan Mehndiratta read out Secretary General's report and Dr. Goutam Ganguly gave the vote of thanks.



Inaugural Program ECON 2014

Presidential Oration - ECON 2014 Kolkata

Therapeutic drug monitoring of Antiepileptic Drug - A level headed approach

Dr V.V. Nadkarni M.D. (Medicine) D.M (Neuro) F.I.A.N.

Therapeutic drug monitoring (TDM) has a positive impact on clinical outcome in epilepsy for the older & newer generation antiepileptic drugs (AEDs) & has a valuable role in guiding patient management, provided the drug concentrations are measured with clear indication & critical interpretation.

In 1900 phenytoin & phenobarbitone came into clinical use for epilepsy. In 1960 AED monitoring started with the pioneering work of Buchthal et. al and TDM which was initially developed for research purposes rapidly expanded into established analytical laboratory activity by 1970. In India, TDM was introduced in 1980 in the clinicopharmacological unit of KEM hospital, Mumbai.

Application of TDM requires adequate knowledge of pharmacokinetics & pharmacodynamic properties of AED. The concept of TDM is based on the fact that drug / dose concentration relationship is a good predictor of drug response at the receptor site with correlation to optimal seizure control.

Type of sample & timing of sampling & assay

There is a clear relationship between drug doses & drug concentration with pharmacological effects, so that lower drug concentration is likely to produce insufficient effect with break through seizures & higher concentrations are associated with adverse effects. TDM estimates total plasma concentration i.e. free drug & protein bound drug routinely measured in serum, while free drug is measured in salivary matrix. The latter is indicated in diseases where protein binding of the drug is affected i.e. pregnancy, elderly and other pathological states like hepatic & renal diseases. Free fractions increase in these circumstances can cause toxicity. Saliva has been advocated as an alternative matrix to serum for estimation of free drug concentration. Since 1980 this is the matrix of choice for children with disabilities. Analytical methods for TDM are High Performance Liquid Chromatography (HPLC) assay technique and Enzyme Multiplied Immune assay technique (EMIT). Emit assays are popular in private practice and HPLC is applied in research laboratory of medical colleges.

Terminology - when to order & how to order?

The clinician who orders the drug levels should understand the terminology used i.e. reference range,



target range and therapeutic ranges. Reference range is defined as the range of the drug concentration with a lower limit below which therapeutic response is unlikely & upper limit above which toxicity occurs. Therapeutic range is defined as a range of concentration in which a given person achieves best response & for majority patients this is within the reference range. Therapeutic range will be useful for management decision should modification in clinical status occur e.g. if seizures subsequently recur in the same patient with subtherapeutic concentration, an increment of dose of the AED is indicated.

The clinician should order the drug sample with proper timings for evaluation & treatment. In case of drugs with long half lives such as Phenobarbital and zonisamide, samples can be collected at any time of the day. In the case of Carbamazepine, valproic acid and lamotrigine, drugs with short half lives, ideal blood sampling time is immediately before the next oral dose (trough) & second sample taken at expected time of peak. If patients present with overdose, sampling is done immediately. Oral absorption of newer AEDs is rapid & efficient up to 85 – 90% with negligible protein binding and have faster elimination with short $\frac{1}{2}$ life. (Exceptions are pro drugs like Oxcarbazepine which is metabolized to 10 Hydroxy-Carbamazepine in which case TDM needs to be interpreted with caution.)

Population at risk - Infants, Children, Pregnant women & Elderly

There are special clinical situations where TDM plays an important role such as in patients with

Recommendations for slow titration and laboratory testing

| AED | Needs slow titration (weeks to reach therapeutic dose)* | Needs for laboratory testing** | Therapeutic drug monitoring *** | Average dose in adults in mg/day | Plasma levels |
|----------------|---|--------------------------------|---|----------------------------------|---------------|
| Carbamazepine | Yes (~4 weeks) | Maximal | Useful | 600 | 4 – 12 |
| Clobazam | Yes (~4 weeks) | Minimal | Not generally useful | 20 | 0.03 – 0.3 |
| Clonazepam | Yes (~4 weeks) | Minimal | Not generally useful | 1 | 0.02 – 0.07 |
| Lamotrigine | Yes (~8 weeks) | Maximal | Very useful in pregnancy and hormonal contraception | 200 | 2.5 – 15 |
| Levetiracetam | No or minimal (0–2 weeks) | Minimal | Not recommended | 1000 | 12 – 46 |
| Oxcarbazepine | Yes (~4 weeks) | Maximal | Not generally useful | 800 | 3 – 35 |
| Phenobarbitone | Yes (~6 weeks) | Minimal | Useful | 100 | 10 – 40 |
| Phenytoin | Yes (~4 weeks) | Maximal | Very useful | 300 | 10 – 20 |
| Topiramate | Yes (~6 weeks) | Maximal | Useful particularly in co-medication | 150 | 5 – 20 |
| Valproate | Yes (~4 weeks) | Maximal | Not generally useful | 1000 | 50 – 100 |
| Zonisamide | Yes (~4 weeks) | Maximal | Useful | 300 | 10 – 40 |

difficult- to- treat epilepsy. TDM helps in determining the required dose increments.. In patients on polytherapy who exhibitsigns of overdose, TDM can aid in determining which drug is more responsiblefor causing toxicity. Children represent a special population for TDM. In infants, pharmacokinetics of AEDs includes short half lives & higher clearance & therefore, higher doses are needed to achieve the same drug concentration compared to adults. In neonates, phenobarbitone & phenytoin clearance is quite low during the first week of life, & in older infants drug metabolism rapidly accelerates to reach high values & hence it is essential to monitor AED concentration in newborns. Pharmacokinetics interaction between AEDs & other medication can alter the drug levels in infants..

Women with epilepsy in the pregnancy period have altered metabolism & hemodynamic changes which causes lower plasma drug concentration with decreased protein binding and increased clearance of AED. Increased metabolism of conventional AED occurs due to induction of hepatic enzyme - cytochrome P 450 pathway. However drugs like lamotrigine undergo hepatic glucuronidation catalyzed by UGT1A4 and hence does not induce Cytochrome P 450 pathwayNeedless to say that non compliance of pregnant women with epilepsy is a major issue which needs drug monitoring . Women with epilepsy face severe anxiety about fetal toxicity related to AED which causes the mothers to withdraw the medicines abruptly.

Maternal serum concentration in pregnancy reflects therapeutic & adverse effects in the mother & also to some extent, the risk of drug exposure to embryo or fetus.TDM during pregnancy aims at

facilitating dosing. Several studies have demonstrated pronounced alteration in pharmacokinetics of lamotrigine during pregnancy with a fall of 30 % of pre-pregnancy concentration which leads to increased seizures. Therefore, a pregnant woman with epilepsy on lamotrigine 300 mg p. /day needs 900 mg /day in the third trimester. . to 900 mg Post natally, the dose of lamotrigine has to be reduced to prevent lamotrigine toxicity in the infant because lamotrigine gets secreted in the breast milk. Older AEDs like carbamazepine, valproate and phenytoin are highly protein bound and hence not secreted in very high concentrations in breast milk At times, there may be a need to monitor the AED level in the plasma of infants. The breast milk and maternal plasma ratiomay also need to be monitored. For example, since glucuronodation is slow in neonates there is a high risk of lamotrigine toxicity.The breast milk to maternal plasma ratio(M/P) should be less than one for avoidance of toxicity in infants. Levetracetam and Topiramate are good drugs with low M/P ratio. Infants of mothers taking Phenobarbitone should be observed for somnolence as exposure to infants is almost 100% with this drug.

Elderly persons who are taking PHT, CBZ, VPA demonstrate decreased protein binding, low clearance & increased $\frac{1}{2}$ life with advancing age. Measurement of unbound free drug is essential for effective management. Elderly PWEs need lower doses & longer dosing intervals.

To conclude, TDM has been used in the last 50 years as the best tool for optimizing epilepsy management but it should always be interpreted in the clinical context.

Treat the patient and not the serum concentration.

Bone Health and Epilepsy

Dr. Bindu Menon



Epilepsy is a chronic neurological condition requiring long term use of anticonvulsants. Chronic use of antiepileptics affects bone health. Bone, a connective dynamic tissue, undergoes continuous remodeling throughout life. Bone continuously renews itself by resorption and formation. Resorption is removing the old bone through the bloodstream which is done by osteoclasts. Osteoblasts initiate new bone formation. Osteocytes monitor bone mechanical stresses. All this together helps to keep our bones strong. For this the bone resorption and formation should match each other, so that the amount of bone removed always equals the amount of new bone formed. This balance is made possible by various hormones in our bodies; including vitamin D. Calcium is essential for healthy bones. Vitamin D is needed by the body to absorb calcium. However with age, resorption often exceeds formation making bones weak. Apart from normal aging, long term use of various drugs increase bone loss, of which antiepileptic drugs (AED) play a major role

AED encompasses a group of drugs with different modes of action, of which Phenytoin, phenobarbital, carbamazepine and valproate appear to have the most impact on reducing bone density and increasing bone turnover. The most important mechanism of action is by cytochrome p450 enzyme induction thereby accelerating hepatic microsomal metabolism of vitamin D to polar metabolites other than (25-OH) vitamin D (25-OHD) and increase the metabolism of 25-OHD into biologically inactive products. The other mechanisms are reduced intestinal absorption of calcium, calcitonin deficiency and impaired response to parathyroid hormone. Information on the effect

of bone health for the newer anticonvulsant drugs is not yet clear.

Bone health is important in different age groups. But the high risk groups for bone loss are elderly, immobile, institutionalized patients and postmenopausal women. Women reach peak bone mass by age 25. After 25 women lose 1% of bone each year till menopause. With menopause, women lose 4-5 % of bone each year. Over a life time women lose 45% of vertebral bone and 55% of their femur. Hence clinicians must exercise caution while introducing enzyme inducing AEDs.

The major consequences of these abnormalities are that persons with epilepsy have an increased risk of fracture. The frequency of fractures is two to six times more frequent in patients with epilepsy compared to the general population. Multiple factors likely influence this increased risk, including seizures, a propensity to fall secondary to impaired balance, and reduced bone mineral density (BMD). However, there is an increased risk of unexpected pathological fractures occurring during normal activity. Patients above 40 years, longer duration of AED use, on enzyme inducing AEDs have been found to have significantly lower bone mineral density at clinically relevant fracture risk sites. Pathologic fractures occur in 20 to 40% of patients on AED traditionally thought not to be at risk for osteoporotic fractures. Elderly women are at particular risk and a long term AED use is associated with increased rates of bone loss at the calcaneus and hip. This increases the risk of hip fracture by 29% over 5 years among women age 65 years and older.

Nutrition plays a major role in maintaining bone health. A healthy bone at an old age depends on the stores of nutrient in the bone in the early childhood and adolescent. Low dietary calcium leads to decreased plasma calcium which triggers secondary hyperparathyroidism leading to osteoclast activity and calcium release from bone. The importance of dietary calcium needs to be emphasized in women in preconception period, during pregnancy and during lactation as this affects the health and nutrition of the offspring.

Calcium and vitamin D are essential for the proper development of the bone and skeletal system. Vitamin D is a fat soluble vitamin produced by the body after exposure to ultraviolet (UV-B) rays from the sun. Sunlight is far more likely to provide a person with vitamin D requirement than food is. The food sources of Vitamin D are Salmon, Mackerel, Tuna fish, Sardines, Liver, beef, Swiss cheese, fortified milk and cereals. The diet of the Indian population does not constitute this particular food habit. In most countries

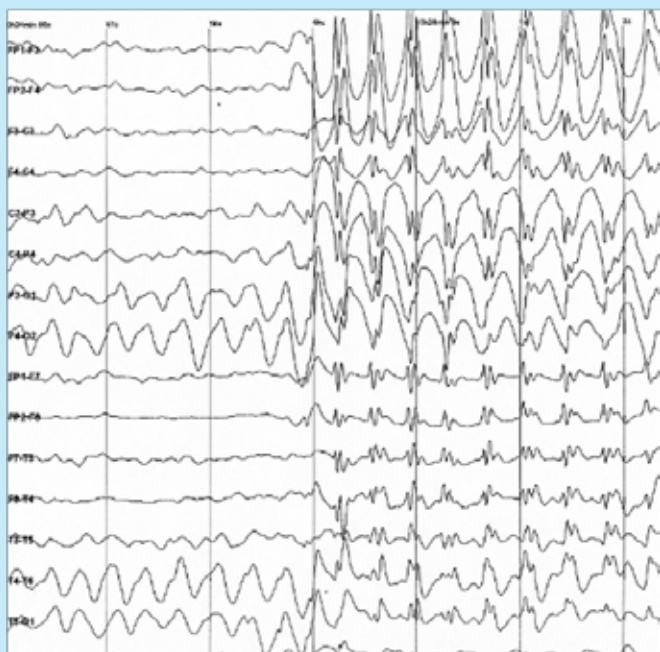
the milk is fortified with calcium, but it is yet to be followed in India. The requirement of calcium varies in various stages of bone growth i.e. during growth spurt, pregnancy and lactation, elderly. The primary sources of calcium in the diet include milk and other dairy products, such as hard cheese, cottage cheese, yogurt, as well as green vegetables, like spinach. While calcium is obtained through diet, the only source of vitamin D is sunlight and fortification of food.

Dual-energy x-ray absorptiometry (DEXA) scan is the current gold standard for diagnosis of osteoporosis. It is important to maintain good bone health practices. Clinicians should discuss the risks associated with AED with patients. Discussion of good bone health practices which should include regular weight-bearing exercise, adequate sunlight exposure, adequate intake of calcium and avoidance of risk factors for osteoporosis such as smoking and alcohol use. High risk patients should be identified before start of AED treatment and evaluated.

Recommended calcium intake (mg/day)

| Group | | | Calcium |
|-----------------------|---------|--|---------|
| Adult | Men | | 600 |
| | Women | | 600 |
| Pregnancy | | | 1200 |
| Lactation | | | 1200 |
| Post menopausal women | | | 800 |
| Infants | | | 500 |
| Children | 1-3yr | | 600 |
| | 4-6yr | | 600 |
| | 7-9yr | | 600 |
| | 10-12yr | | 800 |
| | 13-15yr | | 800 |
| | 16-18yr | | 800 |

New epilepsy treatment offers ‘on demand’ seizure suppression



Generalized 3 Hz spike and wave discharges in a child with childhood absence epilepsy. Credit: Wikipedia.

A new treatment for drug-resistant epilepsy with the potential to suppress seizures ‘on demand’ with a pill, similar to how you might take painkillers when you feel a headache coming on, has been developed by UCL (University College London) researchers funded by the Wellcome Trust.

The treatment, described in *Nature Communications*, combines genetic and chemical approaches to suppress seizures without disrupting normal brain function. The technique was demonstrated in rodents but in future we could see people controlling seizures on-demand with a simple pill.

Epilepsy affects around 50 million people worldwide including 600,000 in the UK and around a quarter of cases are resistant to conventional treatments. Many of these cases could be addressed by the new treatment method, which relies on genetic modification of brain cells to make them sensitive to a

normally inactive compound.

“First, we inject a modified virus into the area of the brain where seizures arise,” explains Professor Dimitri Kullmann of the UCL Institute of Neurology, senior author of the research. “This virus instructs the brain cells to make a protein that is activated by CNO (clozapine-N-oxide), a compound that can be taken as a pill. The activated protein then suppresses the over-excitable brain cells that trigger seizures, but only in the presence of CNO.

“At the moment, severe seizures are treated with drugs that suppress the excitability of all brain cells, and patients therefore experience side effects. Sometimes the dose required to stop seizures is so high that patients need to be sedated and taken to intensive care. If we can take our new method into the clinic, which we hope to do within the next decade, we could treat patients who are susceptible to severe seizures with a one-off injection of the modified virus, and then use CNO only when needed.

“CNO would be given as a pill in the event that patients could predict when seizures were likely to occur. For example, many people with treatment-resistant epilepsy experience clusters of seizures, where severe seizures are preceded by smaller ones. Seizure risk is also high when people are ill, sleep deprived, or at certain times of the menstrual cycle, so these would all be good times to take the pill as a preventative measure. In urgent situations, the compound could be given as an injection. We could even consider a fully automatic delivery system, where CNO was given by a pump, as is done for insulin in some people with diabetes.”

As CNO has a half-life of about a few hours and only affects the pre-treated epileptic parts of the brain, the new method avoids the need to permanently alter the brain or treat the whole brain



with seizure-suppressing drugs. It builds on similar work by Professor Kullmann's group using gene therapy to 'calm down' brain cells, or using light pulses to activate seizure-suppressing receptors in the brain. The new technique works in a similar way but is reversible and avoids the need for invasive devices to deliver light to the brain.

"After the one-off injection into affected areas of the brain, our new technique would require nothing beyond CNO, administered as an injection or a pill, to suppress seizures when required," says Professor Kullmann. "This makes it more attractive than alternative forms of targeted therapy such as surgery to remove the brain region where seizures arise, or gene therapy that permanently alters the excitability of brain cells.

"Although there is currently no evidence that permanently suppressing excitability in a small area affects brain function, we cannot be sure that it would have no impact long-term. Our new method is completely reversible, so if there were any side-effects then people could simply stop taking the CNO pill."

Dr John Williams, head of clinical activities, neuroscience and mental health at the Wellcome Trust said: "Epilepsy is a debilitating condition with limited treatment options available to the 50 million people affected globally. We look forward to seeing how this innovative approach for targeted control of seizure activity might translate into new treatments options for managing and controlling seizures in humans."

Forthcoming Events

10th Asian & Oceanian Epilepsy Congress

7 - 10 August, 2014, Singapore

Congress Website : epilepsysingapore2014.org



8th Latin American Congress on Epilepsy

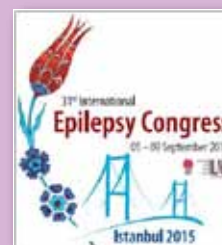
17 - 20 September, 2014, Buenos Aires, Argentina

Congress Website : epilepsycongress.org

International Epilepsy Congress - Istanbul Sept. 2015

Hold the date: The next International Epilepsy Congress will be held on September 5-9, 2015 in Istanbul, Turkey.

Congress Website : www.epilepsyistanbul2015.org



National Epilepsy Day 2013

Trivandrum Chapter

Reported by
Dr. Jayachandran

National Epilepsy day was observed in SCTIMST with a public program and a painting competition for children with epilepsy on 20th November 2013.

The Program in Auditorium II was inaugurated by Dr. Alexander Jacob, Additional Director General

of Police, Kerala. The function was presided by Prof. Jagan Mohan Tharakan, Director, SCTIMST. 14 children with epilepsy participated in the painting competition. The Prize was distributed by the Chief guest Dr. Alexander Jacob and Director, SCTIMST.



Epilepsy camp in Kalpetta, Wayanad

Dr. Jayachandran D. (SCTIMST), Secretary, Indian Epilepsy Association, conducted Epilepsy awareness Program. As part of the National Epilepsy Day an epilepsy camp and awareness camp were organized in Taluk Head quarters Hospital, Kalpetta, Wayanad on 24.11.2013. The program was inaugurated by Shri. M.V. Sreyams Kumar MLA.

68 patients with Epilepsy was examined and counseled by the Dr. Ashalatha R., Associate Professor, Dept. of Neurology, SCTIMST, and team. The awareness program and counseling were done by Dr. Jayachandran. The program was widely covered by Press/media and generated goodwill among the participants and public.



Epilepsy camp in Kalpetta, Wayanad



National Epilepsy Day 2013

Jaipur Chapter

Reported by
Dr. R.K. Sureka

Epilepsy Awareness Programme at Jaipur

On the eve of National Epilepsy Day on 17th November 2013, a public awareness programme was organized by Epilepsy Care & Research Foundation at Swasthya Kalyan Bhawan, Sitapura, Jaipur which was attended by 500 nursing students, homeopathy students, physiotherapy students and teachers and other students.

Dr R K Sureka, Professor, Neurology Department, SMS Hospital, Jaipur & Chairman of the Foundation gave an awareness talk on understanding "Epilepsy". He threw light on various aspects of epilepsy like various misconceptions regarding epilepsy, treatment of epilepsy and special situations like women with epilepsy, children and epilepsy and elderly with

epilepsy. Dr S.S Agrawal, Chairman of Swasthya Kalyan Group of colleges presided over the function.

On this occasion an Exhibition on various aspects of Epilepsy was also organized.

PRESENTATION OF FIRST COPY OF "HANDBOOK OF EPILEPSY – A PRACTICAL GUIDE" TO HON'BLE GOVERNOR OF RAJASTHAN

On the occasion of National Epilepsy Day, the first copy of a hand book written by Dr. R.K.Sureka "HANDBOOK OF EPILEPSY – A PRACTICAL GUIDE" was presented to Her Excellency, Governor of Rajasthan Smt. Margaret Alva at Raj Bhawan. The book has been written as a practical guide especially for general physicians, pediatricians and psychiatrists.



"Presentation of First copy of " HANDBOOK OF EPILEPSY – A PRACTICAL GUIDE " to Her Excellency ,Governor of Rajasthan Smt. Margaret Alva"



"National Epilepsy Day Celebrations at Swasthya Kalyan Bhawan, Sitapura, Jaipur



"Large Audience at Epilepsy Awareness Programme



" Addressing the gathering on National Epilepsy Day"

Tirupati Oration in Epileptology

Reported by
Dr B. Vengamma



The Fourth Oration was organized on 7th December, 2013 at Sri Padmavathi Auditorium, SVIMS at 11.00 am. Sri Y. Srinivasulu Reddy, Member of the Legislative Council of Andhra Pradesh, was the Chief Guest.

Dr. Kurupath Radhakrishnan, Retired Senior Professor (Emeritus), R. Madhavan Nayar Center for Comprehensive Epilepsy Care, Sree Chitra Tirunal, Institute for Medical Sciences and Technology, Trivandrum, Kerala, India delivered the Fourth Oration on the topic "Lessons Learned from Surgery in Epilepsy associated with Neurocysticercosis: A model of Acquired Epilepsy?"

India is one of the countries which is endemic for prevalence of neurocysticercosis around the world,

where poverty, illiteracy and poor sanitation coexist and it reflects as a Biologic Marker of social and economic development of a community.

He also explained briefly about minimum requirement for an epilepsy surgery program.

Success of epilepsy surgery depends upon the completeness of resection of the presumed epileptogenic zone without causing neurological/psychological deficits and also addressing non-medical issues of patients with AED-resistant epilepsy.

In the present era of rapid electronic communication and telemedicine, it has become possible for epilepsy surgery centers to pool their technologies and human resources and partner with centers nationally and internationally.

The erudite lecture was followed by a lively and interesting discussions.

Dr. K. Radhakrishnan was felicitated by the Chief Guest, Dr B. Vengamma, Director, Professor of Neurology, SVIMS and President, IEA, Tirupati Branch and other Senior Members of medical fraternity. He was also presented with a Silver Memento, on behalf of the Department of Neurology, SVIMS, Tirupati.



Moments from ECON 2014



Moments from ECON 2014

