CHAPTER

84

Recent Advances in Epilepsy

Sushil Tandel

INTRODUCTION

With 65 million people affected worldwide, epilepsy is the most common, chronic, serious neurological disease.[1] People with epilepsy suffer from discrimination, misunderstanding, social stigma,[2] and the stress of living with a chronic unpredictable disease that can lead to loss of autonomy for activities of daily living. Although epilepsy can be successfully treated in most cases, the treatment gap is enormous, especially in low-income and middle-income countries,[3] because antiepileptic drugs are inaccessible or too expensive.[4] Nevertheless, not all patients respond to available medical treatments, with increasing evidence that surgery and other treatments (eg, neurostimulation and diet) can be beneficial. As medicine is an ever changing field, it is customary for the clinicians to stay updated hence here we have focussed on recent advances in the field of epilepsy research.

TERMINOLOGY

Definitions

Seizure is defined by the International League against Epilepsy (ILAE) as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain". While Epilepsy is characterised conceptually as an "enduring predisposition of the brain to generate epileptic seizures, with neurobiological, cognitive, psychological, and social consequences".[5]

Epilepsy is considered to be resolved for individuals who either 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 and off anti-seizure medicines for at least the last 5 years."[6]

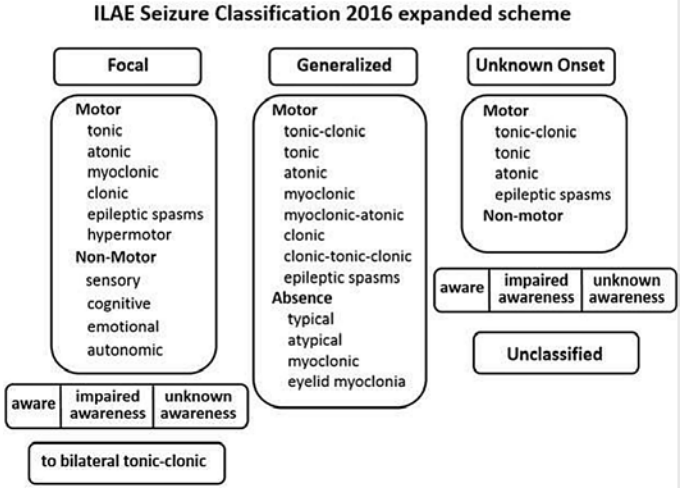

Fig. 1: ILAE Seizure Classification 2016 Expanded Scheme

CLASSIFICATION

Figure 1: Proposed ILAE organisation of epileptic seizures in 2016

The International League Against Epilepsy (ILAE) presents a revised operational classification of seizure types. The purpose of such a revision is to recognize that some seizure types can have either a focal or generalized onset, to allow classification when the onset is unobserved, to include some missing seizure types and to adopt more transparent names.Because current knowledge is insufficient to form a scientifically-based classification, the 2016 classification is operational (practical) and based upon the 1981 Classification, extended in 2010. Changes include: 1. "partial" becomes "focal"; 2. Seizures of unknown onset can still be classified; 3. Awareness is used as a classifier of focal seizures; 4. The terms dyscognitive, simple partial, complex partial, psychic, secondarily generalized are eliminated; 5. Focal tonic, clonic, atonic, myoclonic and epileptic spasms seizure types are recognized, along with bilateral versions of these seizure types. 6. Addition of new generalized seizure types: absence with eyelid myoclonia, myoclonic absence, myoclonic-atonic, clonic-tonic; clonic, epileptic spasms. Epileptic spasms can thus be focal, generalized or unknown. 7. Bilateral tonic-clonic seizure replaces secondarily generalized seizure. Significance: The new classification does not represent a fundamental change, but allows greater flexibility and transparency in naming seizure types[7].

EPIDEMIOLOGY

The prevalence of active epilepsy is 5–8 per 1000 population in high-income countries and 10 per 1000 population in low-income countries, where even higher rates have been reported in rural areas. These regional differences probably result from differences in risk factors for epilepsy, including infections and inadequate antenatal and perinatal care. Similar differences exist for the incidence of epilepsy: findings from a 2011 meta-analysis17 showed that annual incidence is 45 per 100 000 population in high-income countries and 82 per 100 000 population in low-income and middle-income countries.[8]

Etiology

The increasing role that genetic factors play in the aetiology of the epilepsies has become increasingly apparent but environmental factors, including infection, also play a

critical role. Here, we review some of the recent genetic findings from epilepsy studies.

Epilepsy genetic

New techniques such as whole exome sequencing have helped many new discoveries in genetics. With regards to epilepsy, one exciting project completed in 2013 on patients with Lennox–Gastaut syndrome as two classic forms of epileptic encephalopathies. In addition to what are known currently, the authors found mutations in two new genes, GABRB3 and ALG13, which have previously not been linked to epileptic encephalopathy. It is possible that targeting the function of these genes is pivotal for major breakthroughs in therapeutic approaches.[9]

Febrile seizures

Epileptic encephalopathies are devastating syndromes, which are distinct from the most frequent cause of drug resistant epilepsy—mesial temporal lobe epilepsy. However, some epileptic encephalopathies, such as epileptic encephalopathies due to SCN1A mutations (Dravet syndrome and GEFS plus spectrum epilepsies) share common features with mesial temporal lobe epilepsies. In both epilepsies, febrile seizures are often found in the past medical history raising the question whether they may share some genetic similarities. This has been addressed by a recent study which sheds light on the association of SCN1A, febrile seizures and temporal lobe epilepsy. A recent study done recently revealed a association for mesial temporal lobe epilepsy with hippocampal sclerosis and febrile seizures within an intron of the SCN1A gene.[10]

PRRT2 and LGI1

Another advance in 2013 in epilepsy genetics, has been of new mutations within PRRT2. PRRT2 itself has been discovered in 2012 as the gene underlying paroxysmal kinesigenic dyskinesia with infantile convulsions.[11,12]

HPV16 in focal cortical dysplasia

Focal cortical dysplasias are common pathologies encountered in pharmacoresistant epilepsy. Within the umbrella term of malformations of cortical development, focal cortical dysplasias have been mainly classified according to morphological characteristics. The presence of balloon cells is a defining feature of focal cortical dysplasia type IIB (FCDIIB), yet further characteristerization of ballon cells and their function is warranted.[13]

DIAGNOSIS

Diagnosis of the epileptic nature of a seizure can be based on a precise description of the episode semiology by the patient and witnesses, and might not need any specific investigation. The most important recent advance stems from the availability of smartphones, with which relatives can video-record the seizures. Unfortunately, many doctors lack knowledge of the semiology that allows differentiation between epileptic seizures and other disorders such as convulsive syncope and psychogenic non-epileptic attacks, resulting in much misdiagnosis. Correct diagnosis of the underlying epilepsy syndrome needs different investigations depending on the suspected disorder.

Family and personal history, age of onset, seizure type, neurological and cognitive status, 12-lead ECG to rule out cardiac abnormalities, and an interictal EEG are mandatory. A brain MRI is generally needed, except for patients presenting with typical syndromes such as childhood or juvenile absence epilepsy, juvenile myoclonic epilepsy, or self-limited childhood epilepsy with centrotemporal spikes. Blood tests, lumbar puncture, and other investigations can be helpful when specifi c causes are suspected.

Major diagnostic advances over the past decade include improved imaging technology and application of epilepsy targeted protocols for image acquisition and analysis (including three-dimensional FLAIR and voxel-based analyses of multiple contrasts), allowing detection of previously unrecognised subtle epileptogenic lesions; identification of new forms of autoimmune encephalitis, including those associated with anti-NMDA receptors,49 anti-GABAB receptors,50 and antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein (anti-Lgi-1), and contactin-associated protein-2 (anti-Caspr2);and application of genetic advances (including array comparative genomic hybridisation, candidate epilepsy gene panels, and whole-exome sequencing), leading to discovery of new gene mutations in rare epileptic disorders (either sporadic or familial).[8]

MANAGEMENT

Pharmacotherapy

There have been lots of advances in medical management of epilepsy. Since the 1990s, 15 new AEDs have been added to the pharmacologic armamentarium of epilepsy. These have been separated into second- and third-generation AEDs; the former include felbamate, gabapentin, lamotrigine, levetiracetam,oxcarbazepine, pregabalin, tiagabine,topiramate, vigabatrin, and zonisamide.

Third-generation AEDs introduced in the last 5 years include lacosamide, (LCM), rufinamide (RFN), ezogabine (EZG), eslicarbazepine (ESL), and perampanel (PER). These AEDs will be reviewed in brief below:

1. Lacosamide-LCM is an AED that enhances the slow inactivated state of voltage-gated sodium channels (VGSCs) [5],LCM recently received monotherapy approval by the U.S. Food and Drug Administration (FDA) in 2014 for focal epilepsy. Common side effects include dizziness, ataxia, double vision, nystagmus, and nausea. LCM should be used with caution in patients who have known cardiac conduction problems, such as first-degree atrioventricular (AV) block, second-degree or higherAVblock and sick sinus syndrome without pacemaker, or who are on concomitant medications that prolong PR interval.
2. Rufinamide-RFN is a structurally unique triazole

derivative that prolongs the inactive state of sodium channels and slows sodium channel recovery. Although it has been shown to have efficacy in focal epilepsy, it is used primarily in the treatment of drop attacks in Lennox Gastaut Syndrome (LGS).

3. Ezogabine-First neuronal potassium channel opener developed for the treatment of epilepsy acts by enhancement of potassium currents mediated by KCNQ ion channels, thereby reducing hyper excitability. Also potentiates GABA-A receptors via activation of beta 1 & beta 2 subtype of GABA receptor and weakly blocks sodium and calcium channels.Was FDA approved in 2011 as an adjunctive treatment in refractory partial-onset seizures.

4. Eslicarbazepine- Third generation AED which is an effective component of carbamazepine with, fewer cognitive and psychiatric adverse effects.It crosses BBB more effectively, lacks a toxic epoxide unlike its prodrug and has minimal interaction with the cytochrome P450 liver enzymes. In Nov 2013 US FDA approved it as an adjunctive treatment for partial onset seizures.

5. Parampanel-First-in-class drug, a highly selective, non competitive AMPA type glutamate receptor antagonist which was FDA in 2012 approved for treatment of refractory partial-onset seizures in patients 12 years and older, in the dose 4 – 12 mg OD. It has boxed warning about the risk for serious neuropsychiatric events.

New drugs in pipeline

Drugs decreasing neuronal excitation

A. Blockade of sodium channel

Brivaracetam

Carisbamate

B. Inhibition of glutamate release/ AMPA antagonist

- NS 1209
- BGG 492

Drugs enhancing neuronal inhibition

- Ganalaxone
- Stiripentol
- CPP 115
- Valrocemide

Novel agents

1. Anti-inflammatory: Belnacasan (VX 765)
2. Pro-drug of Valproic acid: SPD 421, Valnoctamide
3. Chloride importer blockade: Bumetanide
4. Drugs acting on potassium channels

- YKP 3089
- ICA 105665

5. Melatonin
6. 5HT receptor agonist: Naluzotan.[14]
7. Cannabidiol (partial agonist of central cannabinoid receptor type 1 (CB1) receptors)[15]

Novel non-drug treatments for epilepsy

Despite advances in imaging and the accumulation of neurological and surgical experience,20–40% of patients with epilepsy are considered refractory to medical treatment.1 Less than 50% of these are candidates for focal resective surgery, with rates of long-term seizure freedom ranging from 30% to 60% depending on the operation.2 However, there is widespread agreement that there remains great potential to improve nonpharmacological management, to achieve either better seizure control or complete seizure freedom. Few non-pharmacological methods which are being used world-wide are described below.

NEUROABLATION

Radiofrequency (RF) thermo coagulation

This procedure is done using a RF generator connected to the electrode contacts. It is well tolerated by the patient and does not require general anaesthesia. Multiple sites can be lesioned, with realtime clinical and electrophysiological feedback. Finally, this method does not preclude the possibility of subsequent conventional open surgery. One disadvantage with this technique is that RF thermocoagulation is known to be an inherently imprecise mode of thermal energy delivery.

MR-guided focused ultrasound

Magnetic resonance-guided focused ultrasound surgery (MRgFUS) is an accurate method of delivering high doses of transcranial ultrasound energy to a discrete intracranial focal point. consists of a clinical 3 T MRI, with a transcranial hemispheric array transducer that has 1024 ultrasound elements.

Laser ablation

Ablation can also be achieved by MRI-guided laser interstitial thermal therapy (MRgLITT). The commercially available Visualase Thermal Therapy System combines a 15W 980 nm diode laser and cooled laser application system with an image processing workstation. The applicator is inserted to reach the target by a stereotactic method, and laser treatment is applied in the MR scanner, with MR thermal imaging to visualise the thermal ablation. MRgLITT avoids the complications associated with radio surgery. The ablation is more precise than that achieved with RF thermo coagulation.

Stereotactic radio-surgery

(SRS) is a well-established technique that uses focused ionising radiation to target deep-seated lesions, sparing damage to surrounding tissue. The ionising radiation breaks chemical bonds and results in the production of free radicals. Ionising radiation can be generated by proton beam accelerators and photon accelerators. The

most widely used sources of ionising radiation are photon accelerators, such as Cyberknife and Gamma Knife.

NEUROMODULATION

Functional neurosurgery refers to the surgical manipulation of brain behaviour by the stimulation or removal of a population of neurones.This includes:

VAGAL NERVE STIMULATION

This is a well-established palliative treatment for epilepsy, in patients who are not candidates for resective surgery. Although VNS is unlikely to offer any advance in epilepsy surgery, the elucidation of the mechanism of action may have important consequences for other related treatments. Current evidence points towards a deactivation of the nucleus of the solitary tract, with widespread projections to the dorsal raphe nucleus, locus coeruleus, hypothalamus, thalamus, amygdala and hippocampus.

Trigeminal nerve stimulation Trigeminal nerve stimulation (TNS) is similarly used for deactivation of certain brain nuclei.

DEEP BRAIN STIMULATION

There is a long history of interest in the use of deep brain stimulation (DBS) for epilepsy control. The postulated mechanism of action is by interrupting the propagation of seizure activity, or by increasing the overall seizure threshold. Multiple targets have been put forward, centred in and around the circuit of Papez. The current results with DBS for the treatment of epilepsy remain modest, even accounting for the difficult patient group with highly refractory epilepsy.

CLOSED-LOOP LOCAL DRUG DELIVERY

It is an attractive possibility that localised intracerebral delivery of antiepileptic drugs (AED) can improve the efficacy of pharmacological treatment of epilepsy, without systemic side effects.[36] Several groups are, therefore, engaged in research developing automated local drug delivery systems, comprising of seizure detection technology coupled with intracranial delivery of AED.[16]

Thus, epilepsy surgery remains a significantly underused resource. It is often perceived as a treatment of last resort. Perhaps the most important advance for the future would be to increase awareness in the general population, and education among health professionals, on the safety and efficacy of epilepsy surgery as an early intervention in medically refractory focal epilepsy.

CONCLUSION

There continue to be considerable advances in epilepsy research that will possibly translate into therapies to prevent epilepsy and its co-morbidities and to treat people with pharmaco-resistant epilepsy. However, despite the size of the problem (over 50 million people with epilepsy worldwide of whom 30 % do not respond adequately to our present therapies), epilepsy research remains poorly funded, and there is a continued need for investment.

REFERENCES

1. Thurman DJ, Beghi E, Begley CE, et al, and the ILAE Commission on Epidemiology. Standards for epidemiologic studies and surveillance of epilepsy. *Epilepsia* 2011; 52 (suppl 7): 2–26.
2. Quintas R, Raggi A, Giovannetti AM, et al. Psychosocial difficulties in people with epilepsy: a systematic review of literature from 2005 until 2010. *Epilepsy Behav* 2012; 25:60–67.
3. Meyer AC, Dua T, Ma J, Saxena S, Birbeck G. Global disparities in the epilepsy treatment gap: a systematic review. *Bull World Health Organ* 2010; 88: 260–66.
4. Cameron A, Bansal A, Dua T, et al. Mapping the availability, price, and aff ordability of antiepileptic drugs in 46 countries. *Epilepsia* 2012; 53:962–69.
5. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: defi nitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005; 46:470–72.
6. Fisher R, Acevedo C, Arzimanoglou A, et al. A practical clinical definition of epilepsy. *Epilepsia* 2014; 55:475–82.
7. Scheffer IE, French J, Hirsch E, Jain S, Mathern GW, Moshé SL, Perucca E, Tomson T, Wiebe S, Zhang YH, Zuberi SM. Classification of the epilepsies: New concepts for discussion and debate—Special report of the ILAE Classification Task Force of the Commission for Classification and Terminology. *Epilepsia Open* 2016 Jul 1.
8. Solomon L Moshé, Emilio Perucca, Philippe Ryvlin, Torbjörn Tomson.Epilepsy: new advances.www.thelancet.com.Published online September 24, 2014 http://dx.doi.org/10.1016/S0140-6736(14)60456-6.
9. Allen AS, Epi4 K Consortium, Epilepsy Phenome/Genome Project et al. De novo mutations in epileptic encephalopathies. *Nature* 2013; 501:217–221. doi:10.1038/nature12439.
10. Kasperaviciute D, Catarino CB, Matarin M et al. Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A. *Brain* 2013; 136:3140–3150.
11. Lee H-Y, Huang Y, Bruneau N et al. Mutations in the gene PRRT2 cause paroxysmal kinesigenic dyskinesia with infantile convulsions. *Cell Rep* 2012; 1:2–12. doi:10.1016/j.celrep.2011.11.001 8.
12. Becker F, Schubert J, Striano P et al. PRRT2-related disorders: further PKD and ICCA cases and review of the literature. *J Neurol* 2013; 260:1234–1244. doi:10.1007/s00415-012-6777.
13. Chen J, Tsai V, Parker WE et al. Detection of human papillomavirus in human focal cortical dysplasia type IIB. *Ann Neurol* 2012; 72:881–892. doi:10.1002/ana.23795.
14. Enrique Serrano and Andres M. Kanner. Recent treatment advances and novel therapeutic approaches in epilepsy. F1000Prime Reports 2015, 7:61 (doi:10.12703/P7-61).
15. Saipetch C, Sachs E, Haneef Z. Epilepsy Five new things. Neurology: Clinical Practice 2016 Aug 3:10-212.
16. Nowell M, et al. Advances in epilepsy surgery .J Neurol Neurosurg Psychiatry 2014;85:1273–1279. doi:10.1136/jnnp-2013-30706.