

Epileptic Encephalopathies: New Genes and New Pathways

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Abstract Epileptic encephalopathies represent a group of devastating epileptic disorders that occur early in life and are often characterized by pharmaco-resistant epilepsy, persistent severe electroencephalographic abnormalities, and cognitive dysfunction or decline. Next generation sequencing technologies have increased the speed of gene discovery tremendously. Whereas ion channel genes were long considered to be the only significant group of genes implicated in the genetic epilepsies, a growing number of non-ion-channel genes are now being identified. As a subgroup of the genetically mediated epilepsies, epileptic encephalopathies are complex and heterogeneous disorders, making diagnosis and treatment decisions difficult. Recent exome sequencing data suggest that mutations causing epileptic encephalopathies are often sporadic, typically resulting from de novo dominant mutations in a single autosomal gene, although inherited autosomal recessive and X-linked forms also exist.

In this review we provide a summary of the key features of several early- and mid-childhood onset epileptic encephalopathies including Ohtahara syndrome, Dravet syndrome, Infantile spasms and Lennox Gastaut syndrome. We review the recent next generation sequencing findings that may impact treatment choices. We also describe the use of conventional and newer anti-epileptic and hormonal medications in the various syndromes based on their genetic profile. At a biological level, developments in cellular reprogramming and genome editing represent a new direction in modeling these pediatric epilepsies and could be used in the development of novel and repurposed therapies.

Keywords Epileptic encephalopathies · Genetics · Treatment · Infantile spasms · Dravet syndrome · Lennox–Gastaut syndrome

Introduction

Approximately 40% of seizures occurring during the first three years of life are due to an epileptic encephalopathy (EE) [1]. The International League Against Epilepsy (ILAE) defines epileptic encephalopathies (EEs) as conditions “in which the epileptiform abnormalities are believed to contribute to progressive disturbance in cerebral function” [1]. This implies that not only refractory seizures, but also that the severe epileptiform discharges seen in the EEG background contribute to the progressive decline of cerebral function. The three main features of EEs are: refractory seizures, severe EEG abnormalities, and developmental delay/regression or intellectual disability.

Strong support for the genetic role in epilepsies comes from twin studies that have shown concordance rates to be consistently higher in monozygotic twins in comparison with dizygotic twins [2, 3]. Idiopathic epilepsy, often referred to as epilepsy with no underlying structural brain lesion or other neurological signs or symptoms, is presumed to be genetic (either single gene or multi-genic), and several single gene causes have been identified. In contrast, EEs are classified as symptomatic (given the developmental impairment), and epidemiological evidence suggests that many of these are likely to be sporadic disorders. Recent evidence, particularly discoveries enabled by exome sequencing and whole genome CNV (copy number variant) analyses, has identified de novo dominant mutations as a common etiology (supporting the sporadic nature of the EEs), although less commonly inherited autosomal recessive

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and X-linked forms also exist [4]. This article reviews the clinical presentation, genetic etiologies and treatment approaches for some of the key EEs.

Clinical Presentation and Semiology of EEs

Early Infantile EE (EIEE) or Ohtahara Syndrome

EIEE is one of the most severe early onset epileptic encephalopathies. Ohtahara syndrome (OS) presents within the first 3 months of life, and in the majority of reported cases, within the first 10 days of life. Onset may occur as early as the first hour after delivery, and in retrospect some mothers report movements consistent with seizures in utero [5]. Tonic spasms are the most common seizure type but other semiologies can be present, including focal and myoclonic seizures. The EEG is characterized by burst suppression during both wakefulness and sleep. Ohtahara syndrome can be associated with structural brain malformations, and a subset of cases are associated with specific genetic mutations or metabolic abnormalities. Mutations in several genes have been described in OS, including aristaless-related homeobox (ARX) [6, 7], STXBP1 [8], KCNQ2 [9] and SCN2A [10, 11]. The prognosis is poor, with severe psychomotor retardation often leading to death during infancy. Fortunately, Ohtahara Syndrome is rare [12]. Ohtahara syndrome may evolve into West syndrome and/or Lennox Gastaut syndrome (described below). In one case series, Ohtahara transitioned to West syndrome in 12 out of 16 cases (75%) [13]. Recent genetic discoveries, reviewed below, provide insight into the relationship between Ohtahara and West syndromes.

Infantile Spasms (West Syndrome)

Infantile spasms is the most common form of early onset epileptic encephalopathy. The triad of epileptic spasms, hypsarrhythmia and developmental cessation or regression is referred to as West Syndrome [14–16]. Hypsarrhythmia (Figure 1) is an interictal EEG pattern of high voltage arrhythmic and asynchronous slow and sharp waves with multi-focal spikes and polyspikes.

The epileptic spasms typical of IS are brief seizures with flexion or extension of the arms and legs and/or head and torso that occur in clusters usually upon awakening. IS typically begins between 3 and 7 months of age. The estimated incidence is 2–3.5 per 10,000 live births [17]. Many patients have symptomatic IS (in which another primary disorder leads to IS) and 30–40% have no identified cause despite extensive evaluation. Symptomatic causes of IS include hypoxic-ischemic encephalopathy, perinatal strokes, malformations of cortical development [18], Tuberous Sclerosis [19], and Down syndrome. IS is

a severely disabling condition; many patients develop other seizure types even after complete cessation of spasms [20]. Preliminary evidence indicates that IS is associated with the development of autism to a greater degree than in children presenting with other unprovoked seizure disorders [17, 20–23]. Some evidence indicates an improved prognosis for patients with infantile spasms of unknown cause (IS-UC), and suggests that this prognosis can be improved by early treatment. While there are many symptomatic causes of IS, the shared clinical and electrographic presentation (spasms and hypsarrhythmia on EEG) for IS of both known and unknown cause suggests that the pathophysiology of IS of many forms of IS may involve a common final pathway [24]. The more favorable outcome for early treatment is particularly evident for patients without a known etiology. This suggests that identifying the underlying mechanistic pathways could define more effective treatments to improve outcomes. In terms of treatment type, data from the United Kingdom Infantile Spasms Study (UKISS) suggest superiority of ACTH over vigabatrin for short-term treatment in children with infantile spasms, except in tuberous sclerosis (spasm free outcome in 76 % vs. 54 %) [25, 26]. In tuberous sclerosis, there is convincing evidence that vigabatrin is the treatment of choice with spasm free outcome approximately 74 % [27, 28].

Lennox-Gastaut syndrome (LGS)

Lennox–Gastaut syndrome (LGS) is a severe childhood epileptic encephalopathy characterized by multiple seizure types; tonic seizures are always present along with atonic and atypical absence, focal myoclonic and generalized tonic–clonic seizures [29]. The characteristic EEG shows paroxysms of fast activity and generalized slow spike-and-wave discharges (1.5–2.5 Hz) [30, 31]. Patients have varying degrees of developmental delay with or without regression and often go on to develop autism and intellectual disability [32].

The incidence of LGS is unknown, but is estimated to be between 1% and 10% of all childhood-onset epilepsies, and it is among the most refractory to treatment. LGS typically develops during early childhood, usually between 3 and 5 years of age, but can be observed anytime between 1 and 8 years of age [33].

Six antiepileptic drugs (AEDs) are approved by the US Food and Drug Administration (FDA) for LGS: clonazepam, felbamate, lamotrigine, topiramate, rufinamide and clobazam. The majority of LGS cases require polytherapy and only ~10% of cases undergo full seizure remission with available therapies [34, 35]. Comorbidities including behavioral difficulties and learning disabilities are common, and parents report these as being among the most troubling symptoms

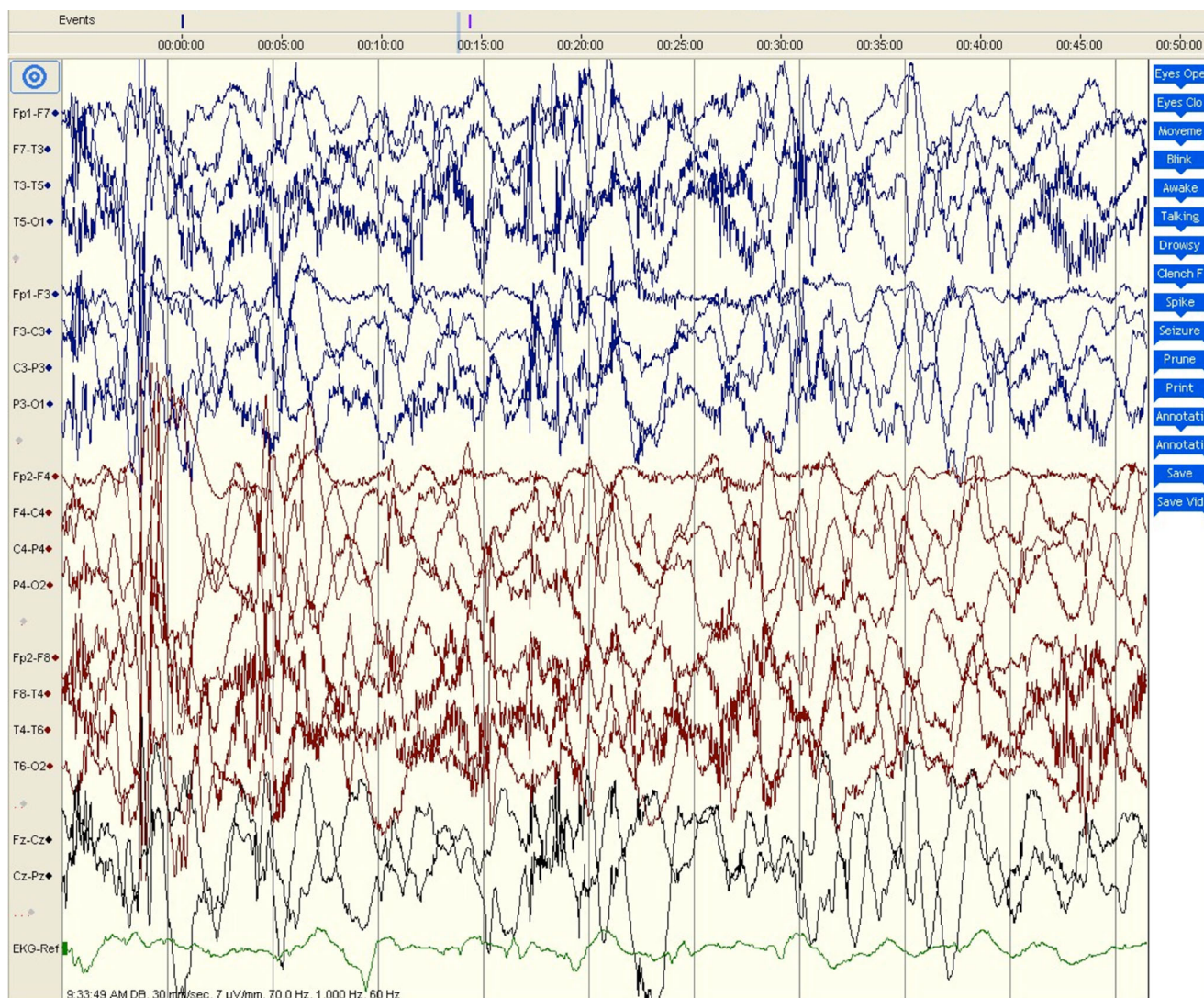


Fig. 1 Hypsarrhythmia: high-voltage arrhythmic and asynchronous slow and sharp waves with multi-focal spikes and polyspikes are pathognomonic for infantile spasms

[36, 37]. Corpus callosotomy may be the preferred therapy for LGS patients whose predominant disabling seizure type is atonic [38]. For other seizure types, vagus nerve stimulation (VNS) offers benefit comparable to callosotomy [39]. Corpus callosotomy is considered to be a palliative procedure, and studies suggest that children with a combination of atonic and tonic seizures benefit from callosotomy to a greater extent than children with generalized tonic-clonic events [40].

Severe Myoclonic Epilepsy in Infancy (Dravet Syndrome)

Dravet syndrome is a severe form of infantile onset epilepsy, generally occurring during the first year of life [41]. The syndrome was first described by Charlotte Dravet as a severe myoclonic epilepsy of infancy (SMEI), characterized by multiple seizure types, prolonged convulsive seizures, frequent episodes of status epilepticus and seizures in the setting of

fever [42]. The incidence of Dravet syndrome is 0.5–1/40,000 and accounts for up to 8 % of all epilepsies in the first 3 years of life. Dravet syndrome is most commonly caused by de novo mutations of SCN1A, encoding the neuronal voltage-gated sodium $\alpha 1$ (Nav1.1) channel [43, 44].

Early Myoclonic Encephalopathy

Early myoclonic encephalopathy is a rare malignant epilepsy syndrome. The syndrome is characterized by erratic myoclonus with or without focal motor seizures [45]. Onset occurs as early as a few hours after birth, and postnatal movements are sometimes reported by the mother to be analogous to those felt at the end of pregnancy. Other types of seizures, including partial seizures, massive myoclonia, and tonic spasms can also occur, usually at 3–4 months of age. In most cases the disease appears to be inherited in an autosomal recessive manner.

There is no effective treatment and the prognosis is poor. Children with early myoclonic epilepsy survive in a persistent vegetative state or die within the first or second year of life [46]. The prevalence of EME is unknown, but appears rare, as only approximately 30 cases are reported. Mutations in *SLC25A22*, which encodes the mitochondrial glutamate/H⁺ symporter, have been reported in several patients with EME [47-50].

Malignant Migrating Partial Seizures of Infancy (MMPSI)

MMPSI or EIEE14 (Early Infantile Epileptic Encephalopathy 14) is a severe form of epilepsy that begins very early in life. Recurrent seizures begin before the age of 6 months and commonly start within a few weeks of birth [51]. The seizures in MMPSI are described as partial (or focal) because the seizure activity is confined to focal brain regions. Seizure activity can appear in multiple locations in the brain, or migrate from one region to another during an episode [52]. Persistent seizures affect growth of the brain and lead to microcephaly [53]. This perturbation of brain development also causes profound developmental delay and intellectual disability. Affected children often regress, losing skills they developed, such as the ability to make eye contact, control head movement, and maintain truncal tone. Seizures are refractory to treatment [53]. If seizures can be controlled for a short period, some milestones may be regained. Some affected children have learned to walk. However, most children with this condition do not develop language skills. Many affected individuals do not survive past infancy or early childhood. Although the prevalence is unknown, only approximately 100 cases of MMPSI have been described in the medical literature. *De novo* gain of function mutations in the *KCNT1* gene have been found in several individuals with this condition and are the most common known cause of MMPSI [54]. A recent study reported a mutation in *SCNA8* in one of 6 MMPSI cases [55].

Landau-Kleffner Syndrome

Landau-Kleffner syndrome (LKS) is an epilepsy syndrome of mid-childhood [56, 57]. The key clinical feature of LKS is the gradual or sudden inability to understand and use spoken language [58, 59]. All children with LKS have EEG abnormalities, and most have continuous or near-continuous spike-waves during slow wave sleep (CSWS). LKS occurs most frequently in normally developing children who are between 3 and 7 years of age, and affects twice as many boys as girls. The cause of LKS is mostly unknown. Mutations in *GRIN2A* (16p13.2) have been reported as a major genetic cause for

LKS and a syndrome known as continuous spikes and waves during slow wave sleep (CSWS; see below) [60, 61]. All of the children with LKS have a normal developmental trajectory until their first seizure or the start of language regression. Although the seizures of LKS may respond well to treatment with anti-epileptic drugs (AEDs), the speech and language difficulties may persist despite seizure control [62].

Continuous Spikes and Waves during Sleep (CSWS)

CSWS is an epileptic encephalopathy of childhood characterized by cognitive or behavioral impairment related to the presence of abundant interictal epileptiform discharges during sleep. After normal or only moderately abnormal baseline development, seizures typically present at 2-4 years of age [16, 63-66]. The seizures are often unilateral, tonic-clonic or clonic, and typically occur out of sleep. At approximately 5-6 years of age, seizures become more frequent, severe, and treatment-resistant with a marked deterioration in seizures, EEG, and accompanying developmental regression. During this stage, the seizures (absence seizures, clonic, tonic-clonic and others) and EEG abnormalities are much less responsive to treatment [64-66]. Spontaneous improvement in seizures and EEG features can occur before puberty, but most patients remain severely developmentally impaired.

Myoclonic Status in Nonprogressive Encephalopathies

Myoclonic status in nonprogressive encephalopathies (MSNE) is an epileptic syndrome characterized by the early onset of continuous diffuse epileptiform abnormalities [67]. Prevalence is unknown, but estimated to be 0.5 % to 1 % of children with severe forms of epilepsy [68, 69]. MSNE is not easy to recognize and should be distinguished from progressive myoclonic epilepsies and other rarely reported infantile myoclonic epilepsies. MSNE has several etiologies including: 1) chromosomal abnormalities including Angelman syndrome (49 %), 2) fetal/neonatal brain hypoxia (20 %), and 3) malformations of cortical development and other structural lesions (31 %) [70, 71]. Prognosis is poor, with progressive neurodegeneration. There is no effective treatment other than benzodiazepines, which transiently interrupt the myoclonic status epilepticus [72].

Genetics of EEs

Genetic factors are believed to play a role in at least 70% of patients with epilepsy [73]. A role for genetics in the etiology of epilepsy includes the action of multiple genetic risk factors in common epilepsies, such as childhood absence epilepsy or juvenile myoclonic epilepsy, and single gene mutations in rare

monogenic epilepsy syndromes. The list of epilepsy genes is rapidly growing, and several of these genes can now be readily screened in clinical practice [74].

A first step towards unbiased gene discovery has been the advent of microarray techniques allowing genome-wide detection of microdeletions and duplications (often referred to as copy number variants; CNV) [75]. This approach has uncovered EE genes such as STXBP1 [8] and GRIN2A [60, 76, 77]. Next Generation Sequencing technologies, including whole exome and whole genome sequencing, have tremendously increased the speed of gene discovery in monogenic epilepsies, leading to a rapid increase in the identification of genetic factors causing epilepsy. Such studies indicate that epileptic encephalopathies may result from highly penetrant mutations in a set of genes, typically arising de novo in the proband. The best example of this is Dravet syndrome (DS), which is caused by mutations in the sodium channel gene (SCN1A) in more than 70% of subjects. Approximately half of SCN1A mutations are truncations, and most DS SCN1A mutations appear to arise de novo [78–81]. Other genes implicated in DS include GABARG2 [82], SCN1B [83], and SCN2A [84]. Several genes have been linked to seizure syndromes that are phenotypically very similar to DS, notably PCDH19 [85, 86] and SCN8A [87]. PCDH19 is X-linked and associated with Epilepsy in Females with Mental Retardation [EFMR] [88]. Recently, a de novo SCN8A mutation was identified in a patient with an infantile epileptic encephalopathy who died of sudden unexplained death in epilepsy (SUDEP) [87]. Other de novo SCN8A mutations were found in a patient with intellectual disability and tonic–clonic seizures, and another patient with epileptic encephalopathy [89–92]. Another recent study identified 6 de novo mutations in HCN1 (Hyperpolarization-activated, cyclic nucleotide-gated channel), which contributes to cationic I_h current in neurons and regulates the excitability of neuronal networks [93]. Individuals with mutations had clinical features resembling those of Dravet syndrome with atypical absence seizures, intellectual disability and autistic features [93].

Glucose transporter 1 deficiency syndrome (GLUT1-DS) is a disorder of brain energy metabolism caused by impaired transport of glucose across the blood–brain barrier, and can be treated with introduction of the ketogenic diet [94–96]. The syndrome was first described in 1991 [97], and the first causative SLC2A1 mutation was identified in 1998 [98, 99]. Subjects with GLUT1 mutations suffer from epilepsy, movement disorders, developmental delay, and acquired microcephaly [97]. The SLC2A1 gene encodes the glucose transporter protein GLUT1, and mutations associated with GLUT1-DS impair transport of glucose across the blood–brain barrier (identified by low glucose in the cerebrospinal fluid on lumbar puncture) [100]. The majority of reported patients (~90 %) harbor a de novo heterozygous mutation in SLC2A1. About 10% of affected individuals have an affected

parent (autosomal dominant inheritance pattern). Autosomal recessive transmission has also been described in rare cases [101, 102].

Whereas ion channel genes were long considered to be the main culprits in genetic epilepsy, a growing number of non-ion-channel genes have been identified, especially in epilepsies associated with abnormal neurodevelopment. A recent study of gene discovery that utilized whole exome sequencing in 264 trios, (a proband and both biological parents) in which the proband had IS or LGS, identified de novo mutations in seven known EE genes (CDKL5, KCNQ2, KCNT1, SCN1A, SCN2A, SCN8A and STXBP1). This study also demonstrated clear evidence of pathogenicity of de novo mutations in two novel genes, GABRB3 and ALG13 in severe childhood epilepsy, and indicated that with further sequencing, several other genes may be implicated [89]. In addition to the overlap genetically between IS and EIEE, this study demonstrated that IS and LGS can have shared etiologies [89]. With the use of multigene panels, additional novel genes have recently been identified such as CHD2, GRIN2A and SYNGAP1 [77, 90]. Other forms of inheritance include mitochondrial, X-linked and male sparing X-linked disorders (e.g. PCDH19 [88], see above).

Phenotype–Genotype Correlations: Broadening the Spectra

The plethora of new genes identified as causes of epilepsy has revealed a previously unappreciated genetic and phenotypic heterogeneity. Mutations in individual genes are now understood to be capable of giving rise to a broad spectrum of phenotype. Conversely, several different genes may cause the same epilepsy syndrome. Therefore, gene discovery must be followed by a careful consideration of the potential phenotypic spectrum. For example, a study of 188 patients with epileptic encephalopathies beginning in infancy demonstrated novel phenotypes associated with SCN1A mutations, enabling clinicians to consider this gene in subjects that would not previously have been considered [103]. Mutations in KCNQ2, encoding the voltage-gated potassium channel subunits Kv7.2, have long been known to be present in 60–70% of families with benign familial neonatal epilepsy (BFNE) [104]. However, a recent study identified 3 newborns with neonatal epileptic encephalopathy associated with de novo mutations in the KCNQ2 gene [105]. Similar observations have been made for other genes causing epileptic encephalopathies. Mutations of the SCN2A gene were originally described in association with benign familial neonatal-infantile seizures (BFNIS) [106–110], but patients with more severe infantile onset epileptic encephalopathy phenotypes have been reported [111, 112]. It was recently determined that the gene STXBP1, responsible for one-third of cases of the early

infantile epileptic encephalopathy Ohtahara syndrome [8, 113, 114], also causes early onset epileptic encephalopathy that does not have the pathognomonic EEG abnormality of Ohtahara syndrome [115]. Many of these children had Infantile Spasms. As different epileptic encephalopathies share overlapping features and may evolve from one to another, as is the case for IS, it is important to evaluate whether the identification of genetic etiology may aid clinicians in predicting the prognosis of such subjects. Results of such studies have major implications for therapeutic choices, prognosis and genetic counseling for children and their families. Genetic discoveries, therefore, support the evolution in clinical practice towards diagnostic screening using large targeted gene panels and eventually exome sequencing. The process of investigating the phenotypic heterogeneity of specific gene defects often produces a distinctive picture of phenotype-genotype correlation that facilitates early diagnosis, treatment and genetic counseling for families [116].

Management of EEs

The major co-morbid features associated with an epileptic encephalopathy are loss of language or other cognitive or developmental abilities, abnormalities of attention and behavior including autistic-like features, psychiatric problems, and sleep disorders [117]. Management is challenging, and requires treatment of seizures as well as these other frequently disabling comorbidities.

Anti-Epileptic Medications (AEDs)

Conventional AEDs typically yield discouraging results in the treatment of EE. However, there are some exceptions, with specific indications in certain epileptic encephalopathy syndromes. Vigabatrin is very effective in West syndrome, particularly when caused by tuberous sclerosis. The drawback is the risk of vigabatrin associated visual loss (VAVL), which has been reported at levels of between 19 and 59 % in pediatric series with a median rate of 33 % [118]. Valproate and lamotrigine (LTG) are considered as a first-line treatment in LGS [33, 119]. Use of rufinamide (RFN) in a randomized controlled trial in patients with LGS led to a significant reduction of seizures, mainly drop attacks, with reduction of the risk of related injuries [120]. Benzodiazepines are also commonly used in the treatment of CSWS, often high dose valium or clobazam. Clobazam is also frequently used in the treatment of Dravet syndrome and LGS amongst other complex epilepsies. It should be noted that there is a small risk of worsening tonic seizures or even precipitating tonic status with benzodiazepine therapy in LGS. In EIEE and malignant migrating partial seizures of infancy (MMPSI) potassium bromide has been used with some positive results. This drug has been also used in Dravet syndrome, with a transitory

seizure control in 30% of patients [121]. As well as newer anti-epileptic medications, there are several older medications that in some cases can be useful in the treatment of epileptic encephalopathies. Sulthiame, a sulphonamide derivative, is a carbonic anhydrase inhibitor and may also act via sodium channels [122]. Felbamate was first approved by the US FDA in 1993 but reports of aplastic anaemia and hepatic failure emerged and led to a marked reduction in its use. However, it has been demonstrated to be effective in a recent study of children with LGS [123]. Potassium bromide is the oldest known anti-epileptic drug and has recently re-emerged as a useful adjunctive treatment for severe early-onset epileptic encephalopathies [123].

Hormonal Treatments

Corticosteroids have long been used for the treatment of a variety of pediatric epilepsy syndromes. There has been one large multicentre trial of the treatment of infantile spasms with corticosteroids, e.g. adrenocorticotrophic hormone (ACTH) [115, 125]. The UKISS trial compared high-dose oral prednisolone or tetracosactide (synthetic analogue of ACTH) with vigabatrin and found that time to initial cessation of spasms was shorter with hormonal treatment [28], although response rate at final assessment was similar between both groups.

Corticosteroids are also widely used in other childhood epilepsies. As there is a lack of evidence regarding choice of corticosteroid, dose and duration of therapy, practice has been guided by expert consensus statements and small case series within specific epilepsy syndromes. The use of corticosteroids has also been described in LKS, Ohtahara syndrome and in LGS, particularly for the treatment of periods of non-convulsive status epilepticus. Only a minority of patients with EE achieve seizure freedom [126, 127]. The main goal of pharmacotherapy is a reduction in the frequency and severity of seizures to improve quality of life [28]. A reduction in seizure frequency can lead to greater alertness, improvements in behavior and cognitive function, a reduction in injuries, less disruption of school, and less impact on social and family relationships. Patients are often on multiple seizure medications, and may also pursue non-pharmacological treatment options, such as hormonal treatments (as discussed above), the ketogenic diet or surgery.

Ketogenic Diet

The ketogenic diet (KD) for the treatment of refractory epilepsy was first reported in 1921 from the observation that brain diseases could be treated by starvation relying on catabolic energy production (mainly fat) *in vivo*. The diet consists of a high ratio of fat, low carbohydrate content and adequate protein so that the body mainly depends on fat to supply energy. Since 1921 a number of clinical and animal studies

have demonstrated utility for KD in a wide range of epilepsies, it is also relatively low cost and associated with small risks [128, 129]. This diet became widely employed after publication of a randomized controlled trial in 145 children [128]. Significant seizure reduction was observed in children with the most severe epilepsies; 38% of children on the diet had a more than 50% reduction in seizure frequency (compared with 6% of controls on a normal diet). [128]. The efficacy of the ketogenic diet varies across epilepsy syndromes; however, it should be considered early in the treatment of children with Dravet syndrome [130]. The ketogenic diet can also be highly efficacious in other genetic and acquired epilepsies, such as lissencephaly and hypoxic–ischaemic encephalopathy [128]. The mechanism of KD in epilepsy is not clear. It has been proposed that KD favorably influences cerebral energetics by increasing cerebral energy reserves along with increased GABA synthesis leading to increased resistance to seizures in ketotic brain tissue along with favorable cognitive effect [131]. The ketogenic diet is particularly indicated in patients who have GLUT1 defects or pyruvate dehydrogenase deficiency as it provides an alternative cerebral energy source [132]. The diet has also been used to treat infantile spasms with some success [133].

Surgery and Neurostimulation

Despite the number of pharmacological options for treatment of epilepsy, many of these patients are largely resistant to pharmacotherapy. Drug-resistant focal epilepsies might evolve into an EE. For these patients with uncontrolled epilepsy, motor and/or neuropsychological deterioration is common. To prevent these secondary consequences, surgery is often considered as a curative or a palliative option.

Early onset focal epilepsies may progress toward West syndrome and later toward an LGS. During childhood, patients with symptomatic focal epilepsies might present with CSWS. Symptomatic cases of focal or hemispheric lesions might improve in response to surgical treatment, such as lobectomy, hemispherotomy, or hemispherectomy, with better results the earlier the surgery is performed. Patients with LGS and drop attacks might improve with callosotomy. However, in the most recent protocols, the use of vagus nerve stimulation (VNS) before callosotomy, is preferred [134]. In children with CSWS that is secondary to a hemi-structural lesion involving the thalamus, lesion resection or hemispheric disconnection has been effective and led to EEG normalization and cognitive improvement [135]. Multiple subpial transection has been performed for a limited number of children with LKS, with case reports of dramatic responses and small case series showing some improvement in, but not normalization of, language function [134].

Future Directions

Recent Advances: Cellular Biology and Genome Editing

Advances in cellular reprogramming have made it possible to generate virtually any cell type from induced Pluripotent Stem Cells (iPSCs). iPSCs provide a particularly attractive model for neurologic disease, where access to live human tissue suitable for culture is extremely limited. Some recent studies have used iPSCs to model epilepsy mechanisms in Dravet syndrome [136]. These data suggest that epilepsy syndrome-specific iPSC-derived neurons are useful for modeling epileptic-like hyperactivity, which offers a platform for screening new antiepileptic therapies.

Another example of using reprogramming technologies is the case of Rett syndrome. Rett syndrome is a devastating neurodevelopmental disorder that occurs once in every 10,000–15,000 live female births. Patients develop normally until 6 to 18 months of age, but then regress rapidly, experiencing a wide range of neurological symptoms, including seizures, ataxia, post-natal microcephaly and stereotypical hand movements with impairment of communication and cognition [137]. Seizure activity is common and occurs in up to 80% of patients. Rett syndrome results largely from functional mutations in the X-linked MECP2 gene [138]. The first Rett syndrome iPSCs (RTT-iPSCs) were generated by the Ellis group [139]. Subsequently, multiple laboratories have derived iPSCs from Rett patients with MECP2 mutations and studied neuronal phenotypes in detail. Neurons from RTT-iPSCs have recapitulated phenotypes observed in both murine models and patients. In vitro phenotypes include reduced soma/nuclear size, lower expression of neuronal markers, and reduced dendrite spine density [140–143]. RTT-iPSC derived neurons also display a reduction in the transient rise of intracellular calcium levels typical of active synapses as well as a decrease in the frequency/amplitude of spontaneous excitatory and inhibitory postsynaptic currents [140]. These models of Rett phenotypes using patient specific RTT- iPSCs provide strong proof of principle of the utility of iPSC in studying RTT. This approach is allowing the research community to study mechanisms of many diseases, including epilepsy, schizophrenia, and autism spectrum disorders. However, the success of in vitro disease modeling depends on the faithful differentiation of pluripotent cells to the cell types that are afflicted. The future of this method will require the development of robust methodologies to produce many additional neuronal subtypes.

When the exact genetic mutations are known for a disease, introducing the given mutations in a standardized ESC or iPSC will facilitate investigation of the effect of mutations in an isogenic background [144]. A number of approaches have been developed to precisely edit the genomes of both ESCs and iPSCs, including Zinc finger nucleases (ZFNs) [145,

[146], the transcription activator-like effector nucleases (TALENs) [147], and clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) [148, 149].

Reprogramming technologies, in combination with robust methodologies to faithfully direct iPSCs to the required cell types, together with recent breakthroughs in genetic modification, provides a renewable source of patient autologous cells for detailed mechanistic study and drug development. Such studies hold great promise for improved understanding and therapeutics for EE.

New Drugs

Zebrafish larvae have emerged as a novel model system for screening pharmacological compounds. A zebrafish mutant was recently described as a simple vertebrate model of a sodium channel mutation recapitulating key features of Dravet syndrome. In this study, Baraban and colleagues identified clemizole as a potential treatment for Dravet syndrome. This study represents another new direction in modeling pediatric epilepsy, and in the future will likely be used increasingly to identify novel therapeutics for other monogenic epilepsy [150].

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