Title
Epileptic Encephalopathies: New Genes and New Pathways

Journal
Neurotherapeutics, 11(4)

ISSN
1933-7213

Authors
Esmaeeli Nieh, Sahar
Sherr, Elliott H

Publication Date
2014-10-01

DOI
10.1007/s13311-014-0301-2

Peer reviewed

Neurotherapeutics (2014) 11:796–806
DOI 10.1007/s13311-014-0301-2

REVIEW

Epileptic Encephalopathies: New Genes and New Pathways

Sahar Esmaeeli Nieh · Elliott H. Sherr

Published online: 30 September 2014

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.

S. Esmaeeli Nieh (✉) · E. H. Sherr (✉)
Departments of Neurology and Pediatrics, University of California, San Francisco, CA, USA
e-mail: EsmaeeliS@neuropeds.ucsf.edu
e-mail: sherre@neuropeds.ucsf.edu

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

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 bellow, 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 with out 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

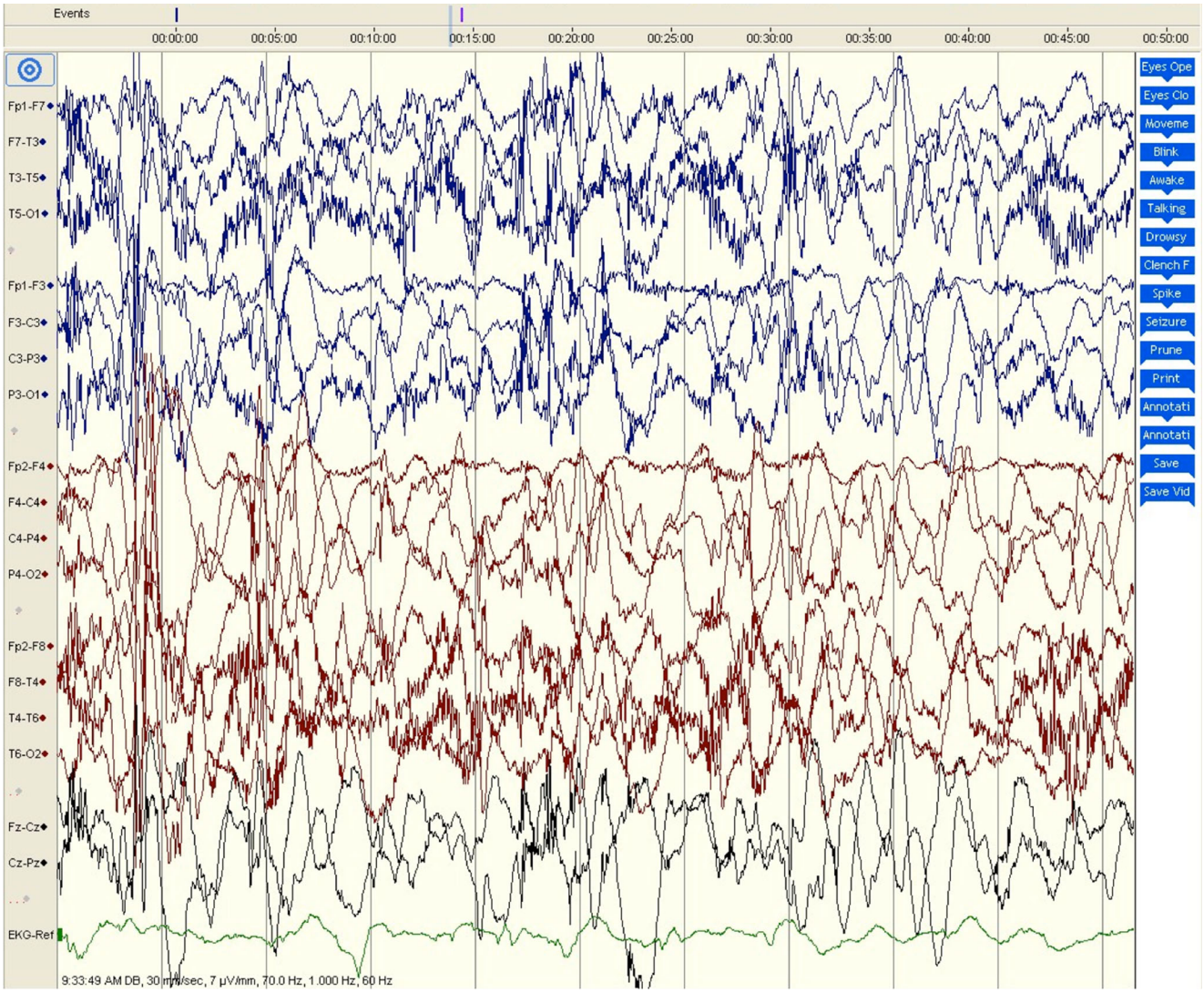

Fig. 1 Hypsarrhythmia: high-voltage arrhythmic and asynchronous slow and sharp waves with multi-focal spikes and polyspikes are pathognomonic for infantile spasms

[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 α1 (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 Ih 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 comorbities.

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. adrenocorticotropic 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 wildly 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].

Acknowledgments We thank Maura Madou (M.D) for patiently reviewing this article.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. Engel J, Jr, International League Against Epilepsy (ILAE). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. Epilepsia 2001;42:796–803.
2. Corey LA, Berg K, Pellock JM, Solaas MH, Nance WE, DeLorenzo RJ. The occurrence of epilepsy and febrile seizures in Virginian and Norwegian twins. Neurology 1991;41:1433–1436.
3. Inouye E. Observations on forty twin index cases with chronic epilepsy and their co-twins. J Nerv Ment Dis 1960;130:401-416.
4. Scheffer IE. Epilepsy genetics revolutionizes clinical practice. Neuropediatrics 2014;45:70-74.
5. Knezevic-Pogancev M. [Ohtahara syndrome—early infantile epileptic encephalopathy]. Med Pregl 2008;61:581-585 [in Serbian].
6. Deprez L, Jansen A, De Jonghe P. Genetics of epilepsy syndromes starting in the first year of life. Neurology 2009;72:273-281.
7. Kato M, Saitoh S, Kamei A, et al. A longer polyalanine expansion mutation in the ARX gene causes early infantile epileptic encephalopathy with suppression-burst pattern (Ohtahara syndrome). Am J Hum Genet 2007;81:361-366.
8. Saitsu H, Kato M, Mizuguchi T, et al. De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. Nat Genet 2008;40:782-788.
9. Kato M, Yamagata T, Kubota M, et al., Clinical spectrum of early onset epileptic encephalopathies caused by KCNQ2 mutation. Epilepsia 2013;54:1282-1287.
10. Nakamura K, Kato M, Osaka H, et al. Clinical spectrum of SCN2A mutations expanding to Ohtahara syndrome. Neurology 2013;81: 992-998.
11. Zerem A, Lev D, Blumkin L, et al. Paternal germline mosaicism of a SCN2A mutation results in Ohtahara syndrome in half siblings. Eur J Paediatr Neurol 2014 Apr 18.
12. Rodgers WP, Durnford AJ, Kirkham FJ, Whitney A, Mullee MA, Gray WP. Interrater reliability of Engel, International League Against Epilepsy, and McHugh seizure outcome classifications following vagus nerve stimulator implantation. J Neurosurg Pediatr 2012;10:226-229.
13. Yamatogi Y, Ohtahara S. Early-infantile epileptic encephalopathy with suppression-bursts, Ohtahara syndrome; its overview referring to our 16 cases. Brain Dev 2002;24:13-23.
14. Auvin S, Lamblin MD, Pandit F, Vallée L, Bouvet-Mourcia A. Infantile epileptic encephalopathy with late-onset spasms: report of 19 patients. Epilepsia 2010;51:1290-1296.
15. Blume WT, Lüders HO, Mizrahi E, Tassinari C, van Emde Boas W, Engel J Jr. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. Epilepsia 2001;42:1212-1218.
16. Anon. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989;30:389-399.
17. Saemundsen E, Ludvigsson P, Rafnsson V. Risk of autism spectrum disorders after infantile spasms: a population-based study nested in a cohort with seizures in the first year of life. Epilepsia 2008;49: 1865-1870.
18. Cappellari M, McDermid RM, Alatalo K, et al. Systematic variation of the stellar initial mass function in early-type galaxies. Nature 2012;484:485-488.
19. Chu-Shore CJ, Major, P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia 2010;51:1236-1241.
20. Riikonen, R., A long-term follow-up study of 214 children with the syndrome of infantile spasms. Neuropediatrics 1982;13:14-23.
21. Watemberg N. Infantile spasms: treatment challenges. Curr Treat Options Neurol 2012;14:322-331.
22. Saemundsen E, Ludvigsson P, Rafnsson V. Autism spectrum disorders in children with a history of infantile spasms: a population-based study. J Child Neurol 2007;22:1102-1107.
23. Jobst BC. Infantile spasms: the devil is in the details, but do we see the forest for the trees? Epilepsy Curr 2011;11:151-152.
24. Swann JW, Moshe SL. On the basic mechanisms of infantile spasms. In: Noebels JL, Avoli M, Rogawski M, Olsen R, Delgado-Escueta A (eds) Jasper's basic mechanisms of the epilepsies. OUP USA, Bethesda, MD, 2012.
25. Riikonen R. A European perspective-comments on "Infantile spasms: a U.S. consensus report". Epilepsia 2010;51:2215-2216.
26. Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. Lancet 2004;364:1773-1778.
27. Darke K, Edwards SW, Hancock E, et al. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multi-centre randomised trial. Arch Dis Child 2010;95:382-386.
28. Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. Lancet Neurol 2005;4: 712-717.

29. Gastraut H, Roger J, Soulayrol R, et al. Childhood epileptic encephalopathy with diffuse slow spike-waves (otherwise known as "petit mal variant") or Lennox syndrome. Epilepsia 1966;7:139-179.
30. Siniatchkin M, Coropceanu D, Moeller F, Boor R, Stephani U. EEG-fMRI reveals activation of brainstem and thalamus in patients with Lennox-Gastaut syndrome. Epilepsia 2011;52:766-774.
31. Pillay N, Archer JS, Badawy RA, Flanagan DF, Berkovic SF, Jackson G. Networks underlying paroxysmal fast activity and slow spike and wave in Lennox-Gastaut syndrome. Neurology 2013;81: 665-673.
32. Arzimanoglou A, Resnick T. All children who experience epileptic falls do not necessarily have Lennox-Gastaut syndrome…but many do. Epileptic Disord 2011;13(Suppl. 1):S3-S13.
33. Arzimanoglou A, French J, Blume WT, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol 2009;8:82-93.
34. Crumrine PK. Management of seizures in Lennox-Gastaut syndrome. Paediatr Drugs 2011;13:107-118.
35. Hancock EC, Cross HH. Treatment of Lennox-Gastaut syndrome. Cochrane Database Syst Rev 2009:CD003277.
36. Purcarin G, Ng YT. Experience in the use of clobazam in the treatment of Lennox-Gastaut syndrome. Ther Adv Neurol Disord 2014;7:169-176.
37. Carmant L, Whiting S. Lennox-Gastaut syndrome: an updateon treatment. Can J Neurol Sci 2012;39:702-711.
38. Maehara T, Shimizu H. Surgical outcome of corpus callosotomy in patients with drop attacks. Epilepsia 2001;42:67-71.
39. Lancman G, Virk M, Shao H, et al. Vagus nerve stimulation vs. corpus callosotomy in the treatment of Lennox-Gastaut syndrome: a meta-analysis. Seizure 2013;22:3-8.
40. Rougier A, Claverie B, Pedespan JM, Marchal C, Loiseau P. Callosotomy for intractable epilepsy: overall outcome. J Neurosurg Sci 1997;41:51-57.
41. Dravet C. The core Dravet syndrome phenotype. Epilepsia 2011;52(Suppl. 2):3-9.
42. Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infancy: Dravet syndrome. Adv Neurol 2005;95:71-102.
43. Hirose S, Scheffer IE, Marini C, et al. SCN1A testing for epilepsy: application in clinical practice. Epilepsia 2013;54:946-952.
44. Meisler MH, O'Brien JE, Sharkey LM. Sodium channel gene family: epilepsy mutations, gene interactions and modifier effects. J Physiol 2010;588:1841-1848.
45. Chen PT, Young C, Lee WT, Wang PJ, Peng SS, Shen YZ. Early epileptic encephalopathy with suppression burst electroencephalographic pattern–an analysis of eight Taiwanese patients. Brain Dev 2001;23:715-720.
46. Ohtahara S, Yamatogi Y. Ohtahara syndrome: with special reference to its developmental aspects for differentiating from early myoclonic encephalopathy. Epilepsy Res 2006;70(Suppl. 1):S58-S67.
47. Molinari F, Raas-Rothschild A, Rio M, et al., Impaired mitochondrial glutamate transport in autosomal recessive neonatal myoclonic epilepsy. Am J Hum Genet 2005;76:334-339.
48. Molinari F. Mitochondria and neonatal epileptic encephalopathies with suppression burst. J Bioenerg Biomembr 2010;42: 467-471.
49. Molinari F, Kaminska A, Fiermonte G, et al. Mutations in the mitochondrial glutamate carrier SLC25A22 in neonatal epileptic encephalopathy with suppression bursts. Clin Genet 2009;76:188-194.
50. Cohen R, Basel-Vanagaite L, Goldberg-Stern H, et al. Two siblings with early infantile myoclonic encephalopathy due to mutation in the gene encoding mitochondrial glutamate/H+ symporter SLC25A22. Eur J Paediatr Neurol 2014 Jul 5.
51. Coppola G, Plouin P, Chiron C, Robain O, Dulac O. Migrating partial seizures in infancy: a malignant disorder with developmental arrest. Epilepsia 1995;36:1017-1024.
52. Nabbout R, Dulac O. Epileptic syndromes in infancy and childhood. Curr Opin Neurol 2008;21:161-166.
53. Coppola G. Malignant migrating partial seizures in infancy. Handb Clin Neurol 2013;111:605-609.
54. Barcia G, Fleming MR, Deligniere A, et al. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. Nat Genet 2012;44:1255-1259.
55. Ohba C, Kato M, Takahashi S, et al. Early onset epileptic encephalopathy caused by de novo SCN8A mutations. Epilepsia 2014;55: 994-1000.
56. Landau WM, Kleffner FR. Syndrome of acquired aphasia with convulsive disorder in children. Neurology 1957;7:523-530.
57. Nakano S, Okuno T, Mikawa H. Landau-Kleffner syndrome. EEG topographic studies. Brain Dev 1989;11:43-50.
58. Rudolf G, Valenti MP, Hirsch E, Szepetowski P. From rolandic epilepsy to continuous spike-and-waves during sleep and Landau-Kleffner syndromes: insights into possible genetic factors. Epilepsia 2009;50(Suppl. 7):25-28.
59. Van Hirtum-Das M, et al. Children with ESES: variability in the syndrome. Epilepsy Res 2006;70(Suppl. 1):S248-S258.
60. Lesca G, Rudolf G, Bruneau N, et al. GRIN2A mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction. Nat Genet 2013;45:1061-1066.
61. Conroy J, McGettigan PA, McCreary D, et al., Towards the identification of a genetic basis for Landau-Kleffner syndrome. Epilepsia 2014;55:858-865.
62. Caraballo RH, Cejas N, Chamorro N, Kaltenmeier MC, Fortini S, Soprano AM. Landau-Kleffner syndrome: a study of 29 patients. Seizure 2014;23:98-104.
63. Loddenkemper T, Fernandez IS, Peters JM. Continuous spike and waves during sleep and electrical status epilepticus in sleep. J Clin Neurophysiol 2011;28:154-164.
64. Nickels K, Wirrell E. Electrical status epilepticus in sleep. Semin Pediatr Neurol 2008;15:50-60.
65. Sánchez Fernández I, Loddenkemper T, Peters JM, Kothare SV. Electrical status epilepticus in sleep: clinical presentation and pathophysiology. Pediatr Neurol 2012;47:390-410.
66. Tassinari CA, Rubboli G, Volpi L, et al. Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. Clin Neurophysiol 2000;111(Suppl. 2):S94-S102.
67. Aicardi J, Chevrie JJ. Myoclonic epilepsies of childhood. Neuropadiatrie 1971;3:177-190.
68. Bureau M, Tassinari CA. Epilepsy with myoclonic absences. Brain Dev 2005;27:178-184.
69. Elia M. Myoclonic status in nonprogressive encephalopathies: an update. Epilepsia 2009;50(Suppl. 5):41-44.
70. Caraballo RH, et al. Myoclonic status in nonprogressive encephalopathies: study of 29 cases. Epilepsia 2007;48:107-113.
71. Dalla Bernardina B, Fontana E, Darra F. Myoclonic status in nonprogressive encephalopathies. Adv Neurol 2005;95:59-70.
72. Khan S, Al Baradie R. Epileptic encephalopathies: an overview. Epilepsy Res Treat 2012;2012:403592.
73. Hildebrand MS, Dahl HH, Damiano JA, Smith RJ, Scheffer IE, Berkovic SF. Recent advances in the molecular genetics of epilepsy. J Med Genet 2013;50:271-279.
74. Thomas RH, Berkovic SF. The hidden genetics of epilepsy-a clinically important new paradigm. Nat Rev Neurol 2014;10: 283-292.
75. Mefford HC, Yendle SC, Hsu C, et al., Rare copy number variants are an important cause of epileptic encephalopathies. Ann Neurol 2011;70:974-985.

76. Lemke JR, Lal D, Reinthaler EM, et al. Mutations in GRIN2A cause idiopathic focal epilepsy with rolandic spikes. Nat Genet 2013;45: 1067-1072.
77. Carvill GL, Regan BM, Yendle SC, et al. GRIN2A mutations cause epilepsy-aphasia spectrum disorders. Nat Genet 2013;45:1073-1076.
78. Wallace RH, Hodgson BL, Grinton BE, et al. Sodium channel alpha1-subunit mutations in severe myoclonic epilepsy of infancy and infantile spasms. Neurology 2003;61:765-769.
79. Fujiwara T, Sugawara T, Mazaki-Miyazaki E, et al. Mutations of sodium channel alpha subunit type 1 (SCN1A) in intractable childhood epilepsies with frequent generalized tonic-clonic seizures. Brain 2003;126:531-546.
80. Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet 2001;68:1327-1332.
81. Nabbout R, Gennaro E, Dalla Bernardina B, et al. Spectrum of SCN1A mutations in severe myoclonic epilepsy of infancy. Neurology 2003;60:1961-1967.
82. Harkin LA, Bowser DN, Dibbens LM, et al. Truncation of the GABA(A)-receptor gamma2 subunit in a family with generalized epilepsy with febrile seizures plus. Am J Hum Genet 2002;70:530-536.
83. Patino GA, Claes LR, Lopez-Santiago LF, et al., A functional null mutation of SCN1B in a patient with Dravet syndrome. J Neurosci 2009;29:10764-10778.
84. Lossin C, Shi X, Rogawski MA, Hirose S. Compromised function in the Na(v)1.2 Dravet syndrome mutation R1312T. Neurobiol Dis 2012;47:378-384.
85. Depienne C, Bouteiller D, Keren B, et al. Sporadic infantile epileptic encephalopathy caused by mutations in PCDH19 resembles Dravet syndrome but mainly affects females. PLoS Genet 2009;5: e1000381.
86. van Harssel JJ, Weckhuysen S, van Kempen MJ, et al. Clinical and genetic aspects of PCDH19-related epilepsy syndromes and the possible role of PCDH19 mutations in males with autism spectrum disorders. Neurogenetics 2013;14:23-34.
87. Veeramah KR, O'Brien JE, Meisler MH, et al. De novo pathogenic SCN8A mutation identified by whole-genome sequencing of a family quartet affected by infantile epileptic encephalopathy and SUDEP. Am J Hum Genet 2012;90:502-510.
88. Dibbens LM, Tarpey PS, Hynes K, et al. X-linked protocadherin 19 mutations cause female-limited epilepsy and cognitive impairment. Nat Genet 2008;40:776-781.
89. Epi4K Consortium; Epilepsy Phenome/Genome Project, Allen AS, et al. De novo mutations in epileptic encephalopathies. Nature 2013;501:217-221.
90. Carvill GL, Heavin SB, Yendle SC, et al. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1. Nat Genet 2013;45:825-830.
91. Rauch A, Wieczorek D, Graf E, et al. Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study. Lancet 2012;380:1674-1682.
92. Vaher U, Nõukas M, Nikopensius T, et al. De novo SCN8A mutation identified by whole-exome sequencing in a boy with neonatal epileptic encephalopathy, multiple congenital anomalies, and movement disorders. J Child Neurol 2013 Dec 18.
93. Nava C, Dalle C, Rastetter A, et al. De novo mutations in HCN1 cause early infantile epileptic encephalopathy. Nat Genet 2014;46: 640-645.
94. Klepper J, Leiendecker B. Glut1 deficiency syndrome and novel ketogenic diets. J Child Neurol 2013;28:1045-1048.
95. Klepper J, Leiendecker B, Riemann E, Baumeister FA. [The ketogenic diet in German-speaking countries: update 2003]. Klin Padiatr 2004;216:277-285 [in German].
96. Klepper J, Scheffer H, Leiendecker B, et al. Seizure control and acceptance of the ketogenic diet in GLUT1 deficiency syndrome: a 2- to 5-year follow-up of 15 children enrolled prospectively. Neuropediatrics 2005;36:302-308.
97. De Vivo DC, Trifiletti RR, Jacobson RI, Ronen GM, Behmand RA, Harik SI. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. N Engl J Med 1991;325:703-709.
98. Klepper J, Leiendecker B. GLUT1 deficiency syndrome—2007 update. Dev Med Child Neurol 2007;49:707-716.
99. Seidner G, Alvarez MG, Yeh JI, et al. GLUT-1 deficiency syndrome caused by haploinsufficiency of the blood-brain barrier hexose carrier. Nat Genet 1998;18:188-191.
100. Klepper J. GLUT1 deficiency syndrome in clinical practice. Epilepsy Res 2012;100:272-277.
101. Klepper J, Scheffer H, Elsaid MF, Kamsteeg EJ, Leferink M, Ben-Omran T. Autosomal recessive inheritance of GLUT1 deficiency syndrome. Neuropediatrics 2009;40:207-210.
102. Rotstein M, Engelstad K, Yang H, et al. Glut1 deficiency: inheritance pattern determined by haploinsufficiency. Ann Neurol 2010;68:955-958.
103. Harkin LA, McMahon JM, Iona X, et al. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain 2007;130:843-852.
104. Soldovieri MV, Boutry-Kryza N, Milh M, et al., Novel KCNQ2 and KCNQ3 mutations in a large cohort of families with benign neonatal epilepsy: first evidence for an altered channel regulation by syntaxin-1A. Hum Mutat 2014;35:356-367.
105. Numis AL, Angriman M, Sullivan JE, et al. KCNQ2 encephalopathy: delineation of the electroclinical phenotype and treatment response. Neurology 2014;82:368-370.
106. Heron SE, Crossland KM, Andermann E, et al. Sodium-channel defects in benign familial neonatal-infantile seizures. Lancet 2002;360:851-852.
107. Berkovic SF, Heron SE, Giordano L, et al. Benign familial neonatal-infantile seizures: characterization of a new sodium channelopathy. Ann Neurol 2004;55:550-557.
108. Striano P, Bordo L, Lispi ML, et al., A novel SCN2A mutation in family with benign familial infantile seizures. Epilepsia 2006;47: 218-220.
109. Herlenius E, Heron SE, Grinton BE, et al. SCN2A mutations and benign familial neonatal-infantile seizures: the phenotypic spectrum. Epilepsia 2007;48:1138-1142.
110. Liao Y, Deprez L, Maljevic S, et al. Molecular correlates of age-dependent seizures in an inherited neonatal-infantile epilepsy. Brain 2010;133:1403-1414.
111. Hackenberg A, Baumer A, Sticht H, et al. Infantile epileptic encephalopathy, transient choreoathetotic movements, and hypersomnia due to a de novo missense mutation in the SCN2A gene. Neuropediatrics 2014;45:261-264.
112. Matalon D, Goldberg E, Medne L, Marsh ED. Confirming an expanded spectrum of SCN2A mutations: a case series. Epileptic Disord 2014;16:13-18.
113. Saitsu H, Kato M, Okada I, et al. STXBP1 mutations in early infantile epileptic encephalopathy with suppression-burst pattern. Epilepsia 2010;51:2397-2405.
114. Milh M, Villeneuve N, Chouchane M, et al. Epileptic and nonepileptic features in patients with early onset epileptic encephalopathy and STXBP1 mutations. Epilepsia 2011;52: 1828-1834.
115. Romaniello R, Zucca C, Tenderini E, et al. A novel mutation in STXBP1 gene in a child with epileptic encephalopathy and an atypical electroclinical pattern. J Child Neurol 2014;29:249-253.
116. Ottman R, Lee JH, Hauser WA, et al., Reliability of seizure classification using a semistructured interview. Neurology 1993;43:2526-2530.

117. McTague A, Cross JH. Treatment of epileptic encephalopathies. CNS Drugs 2013;27:175-184.
118. Maguire MJ, Hemming K, Wild JM, Hutton JL, Marson AG. Prevalence of visual field loss following exposure to vigabatrin therapy: a systematic review. Epilepsia 2010;51:2423-2431.
119. Lemmon ME, Kossoff EH. New treatment options for lennox-gastaut syndrome. Curr Treat Options Neurol 2013;15:519-528.
120. Glauser T, Kluger G, Sachdeo R, Krauss G, Perdomo C, Arroyo S. Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. Neurology 2008;70:1950-1958.
121. Lotte J, Haberlandt E, Neubauer B, Staudt M, Kluger GJ. Bromide in patients with SCN1A-mutations manifesting as Dravet syndrome. Neuropediatrics 2012;43:17-21.
122. Fejerman N, Caraballo R, Cersósimo R, Ferraro SM, Galicchio S, Amartino H. Sulthiame add-on therapy in children with focal epilepsies associated with encephalopathy related to electrical status epilepticus during slow sleep (ESES). Epilepsia 2012;53:1156-1161.
123. Zupanc ML, Roell Werner R, Schwabe MS, et al., Efficacy of felbamate in the treatment of intractable pediatric epilepsy. Pediatr Neurol 2010;42:396-403.
124. Okuda K, Yasuhara A, Kamei A, Araki A, Kitamura N, Kobayashi Y. Successful control with bromide of two patients with malignant migrating partial seizures in infancy. Brain Dev 2000;22:56-59.
125. Verhelst H, Boon P, Buyse G, et al. Steroids in intractable childhood epilepsy: clinical experience and review of the literature. Seizure 2005;14:412-421.
126. Goldsmith IL, Zupanc ML, Buchhalter JR. Long-term seizure outcome in 74 patients with Lennox-Gastaut syndrome: effects of incorporating MRI head imaging in defining the cryptogenic subgroup. Epilepsia 2000;41:395-399.
127. Nunes VD, Sawyer L, Neilson J, Sarri G, Cross JH. Diagnosis and management of the epilepsies in adults and children: summary of updated NICE guidance. BMJ 2012;344:e281.
128. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 2008;7:500-506.
129. Li B, Tong L, Jia G, Sun R. Effects of ketogenic diet on the clinical and electroencephalographic features of children with drug therapy-resistant epilepsy. Exp Ther Med 2013;5:611-615.
130. Thammongkol S, Vears DF, Bicknell-Royle J, et al., Efficacy of the ketogenic diet: which epilepsies respond? Epilepsia 2012;53:e55-e59.
131. Noh HS, Kim YS, Lee HP, et al., The protective effect of a ketogenic diet on kainic acid-induced hippocampal cell death in the male ICR mice. Epilepsy Res 2003;53:119-128.
132. Kossoff EH, Zupec-Kania BA, Armark PE, et al., Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. Epilepsia 2009;50:304-317.
133. Caraballo RH. Nonpharmacologic treatments of Dravet syndrome: focus on the ketogenic diet. Epilepsia 2011;52(Suppl. 2):79-82.
134. Cross JH, Neville BG. The surgical treatment of Landau-Kleffner syndrome. Epilepsia 2009;50(Suppl. 7):63-67.
135. Peltola ME, Liukkonen E, Granström, ML et al. The effect of surgery in encephalopathy with electrical status epilepticus during sleep. Epilepsia 2011;52:602-609.
136. Liu Y, Lopez-Santiago LF, Yuan Y, et al. Dravet syndrome patient-derived neurons suggest a novel epilepsy mechanism. Ann Neurol 2013;74:128-139.
137. Kriaucionis S, Bird A. DNA methylation and Rett syndrome. Hum Mol Genet 2003;12:R221-R227.
138. Amir RE, Van den Veyver IB, et al., Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet 1999;23:185-188.
139. Hotta A, Cheung AY, Farra N, et al. Isolation of human iPS cells using EOS lentiviral vectors to select for pluripotency. Nat Methods 2009;6:370-376.
140. Marchetto MC, Carromeu C, Acab A, et al. A model for neural development and treatment of Rett syndrome using human induced pluripotent stem cells. Cell 2010;143:527-539.
141. Ananiev G, Williams EC, Li H, Chang Q. Isogenic pairs of wild type and mutant induced pluripotent stem cell (iPSC) lines from Rett syndrome patients as in vitro disease model. PLoS One 2011; 6: e25255.
142. Cheung AY, Horvath LM, Grafodatskaya D, et al., Isolation of MECP2-null Rett Syndrome patient hiPS cells and isogenic controls through X-chromosome inactivation. Hum Mol Genet 2011;20: 2103-2115.
143. Kim KY, Hysolli E, Park IH. Neuronal maturation defect in induced pluripotent stem cells from patients with Rett syndrome. Proc Natl Acad Sci U S A 2011;108:14169-14174.
144. Soldner F, Laganière J, Cheng AW, et al. Generation of isogenic pluripotent stem cells differing exclusively at two early onset Parkinson point mutations. Cell 2011;146:318-331.
145. Urnov FD, Rebar EJ, Holmes MC, Zhang HS, Gregory PD. Genome editing with engineered zinc finger nucleases. Nat Rev Genet 2010;11:636-646.
146. Carroll D. Genome engineering with zinc-finger nucleases. Genetics 2011;188:773-782.
147. Joung JK, Sander JD. TALENs: a widely applicable technology for targeted genome editing. Nat Rev Mol Cell Biol 2013;14:49-55.
148. Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science 2012;337:816-821.
149. Mali P, Yang L, Esvelt KM, et al. RNA-guided human genome engineering via Cas9. Science 2013;339:823-826.
150. Baraban SC, Dinday MT, Hortopan GA. Drug screening in Scn1a zebrafish mutant identifies clemizole as a potential Dravet syndrome treatment. Nat Commun 2013;4:2410.