



Neonatal Developmental and Epileptic Encephalopathies

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The new concept of developmental and epileptic encephalopathy is based on the understanding that many genetic epilepsies are associated with developmental impairment as a direct consequence of the genetic mutation, in addition to the effect of the frequent epileptic activity on brain development. As an example, in infants with KCNQ2 or STXBP1 encephalopathy, seizures may be controlled early after onset or cease spontaneously after a few years, but the developmental consequences tend to remain profound. The term “developmental and epileptic encephalopathy” expresses the concept that the genetic defect may be responsible for both the epilepsy and adverse development which is crucial to understanding the disease process for both families and clinicians. The increased use of EEG monitoring, neuroimaging, and metabolic and genetic testing in the Neonatal Intensive Care Unit has greatly improved our understanding of neonatal-onset epilepsies as seen with the syndromes Ohtahara and Early Myoclonic Encephalopathy outlined in the 1970s into distinct etiology-specific electroclinical phenotypes.

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Introduction

Epileptic encephalopathies are conditions in which abundant epileptiform activity interferes with brain development, resulting in cognitive slowing, plateauing, or regression.¹ The concept of epileptic encephalopathy suggests that the epileptic activity itself contributes to the poor neurologic outcome above and beyond what might be expected from the underlying pathology alone. The implication is that amelioration of the epileptiform activity may improve the developmental consequences of these disorders.² However, for some neonatal epilepsies, such as KCNQ2 or STXBP1 encephalopathy, the genetic defect may directly lead to both severe epilepsy and profound intellectual disability as 2 independent dimensions of the phenotype. In severe genetic epilepsies, the developmental consequences may arise more as the direct effect of the genetic mutation than from

the effect of the frequent epileptic activity on development. The relevance of these 2 components, the epileptic component and the developmental component, can vary in the course of neonatal-onset epilepsies. For instance, in some patients with KCNQ2-encephalopathy or STXBP1-encephalopathy, the epilepsy may settle down relatively early, but the developmental consequences may remain profound. These observations, pertinent to many of the genetic encephalopathies, suggested a broadening of the terminology to include the word “developmental,” acknowledging that both aspects may play a role in the clinical presentation. These concepts, highlighted in the last International League Against Epilepsy (ILAE) position paper on the classification of the epilepsies, are crucial to the understanding of the disease processes for both families and clinicians.²

Early Myoclonic Encephalopathy and Ohtahara Syndrome

The International League Against Epilepsy (ILAE) commission on classification and terminology¹ recognizes 3 neonatal electroclinical syndromes: Benign Familial Neonatal Epilepsy (BFNE), Early Myoclonic Encephalopathy (EME), and Ohtahara syndrome (OS). While BFNE is a self-limited form of epilepsy associated in most cases with normal development,

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EME and OS are characterized by a severe disruption of cerebral functions associated with seizures, often intractable. OS and EME were first described more than 50 years ago, in 1976 and 1978, respectively.^{3,4}

The past 20 years have seen the implementation of video-EEG recording in the Neonatal Intensive Care Unit (NICU) which has allowed for a better definition of the different electroclinical phenotypes of neonatal epilepsies. At the same time, significant advances in genetics led to the discovery of new genes in epileptic encephalopathies (ie, *CDKL5*, *KCNQ2*, *KCNT1*), and the evolution of MRI techniques has disclosed underlying malformations that went unnoticed with CT scan. Therefore, under the umbrella of OS and EM distinct electroclinical phenotypes representing new, more discrete, etiology-related syndromes are being increasingly recognized.

EME and OS share the important feature of a burst-suppression pattern (BS) on EEG, though there has been much discussion concerning the specific differences of the BS pattern in each of these syndromes.⁵ BS consists of short periods of high-voltage activity with mixed features including spikes and slow waves, without age appropriate activity alternating with periods of marked background attenuation (Fig. 1).

A main focus of investigation regarding the pathophysiology of OS has been on genetic mutations. Mutations in the X chromosome-linked, *Aristaless*-related, homeobox gene (*ARX*) were initially reported in 9 families with mental retardation (syndromic and nonspecific), various forms of epilepsy, including infantile spasms and myoclonic seizures, and dystonia.⁶ Subsequently, several mutations of the *ARX* gene have been reported^{7,8} and associated with a spectrum of phenotypes, ranging from OS^{9,10} to X-linked Infantile Spasms Syndrome (ISSX).^{6,11}

De novo mutations in the *STXBP1* (Syntaxin Binding Protein 1) gene—also known as Munch18-1 have been found associated with OS.¹² This gene is now considered a major cause of OS even if mutations in *STXBP1* have been implicated in other early onset epilepsies including West syndrome.

After the initial identification of *ARX* and *STXBP1*, other genes have been reported as a cause for OS, including *KCNQ2*, *CDKL5*, and *KCNT1*.¹³⁻¹⁵ While conditions associated with these genes share with OS age at onset, developmental delay, and seizure intractability, they represent specific etiology-related syndromes.¹⁶⁻¹⁸

KCNQ2 Encephalopathy

Characteristic features of *KCNQ2* encephalopathy are early onset of focal tonic seizures, similar to the semiology seen in Benign Familial Neonatal Epilepsy (BFNE),¹⁹ associated with encephalopathy (hypotonia, paucity of spontaneous movements, no visual fixation and altered reactivity). In contrast to BFNE, the neonatal EEG background in *KCNQ2* encephalopathy demonstrates multifocal epileptiform abnormalities with random attenuation or burst-suppression. While seizures tend to remit in early childhood, most children have severe intellectual disability²⁰ exemplifying the concept of

“developmental encephalopathy” as described earlier. This highlights the need for therapeutic approaches in developmental and epileptic encephalopathies addressing, in addition to the epilepsy, the developmental outcome, and ideally targeting the pathophysiology induced by the genetic defect.

As in BFNE, sodium channel blockers such as carbamazepine and phenytoin have been shown to be particularly effective^{17,21} and are now considered an established precision medicine treatment for *KCNQ2*-related epilepsies.²²

More recently, gain-of-function variants (R201H and R201C) have also been reported to cause *KCNQ2* encephalopathy although they are associated with a different phenotype than the loss-of-function variants. In this case, the clinical presentation are not seen in the neonatal period, the clinical presentation is characterized instead by irregular breathing patterns, exaggerated startle responses and nonepileptic myoclonus, but epileptic seizures are not seen.²³

SCN2A-Related Neonatal Epilepsies

SCN2A is also a channelopathy associated with a spectrum of presentations in the neonate, from benign familial neonatal-infantile epilepsy (BFNIE) to neonatal-onset epileptic encephalopathy.²⁴

SCN2A encodes Nav1.2, a major voltage-gated sodium channel in the central nervous system early in development. Nav1.2 is supplanted over time, to some extent, by Nav1.6 (*SCN8A*), which may account for the limited temporal expression of *SCN2A*-associated epilepsy.²⁵ Interestingly, mutations in the *SCN8A* gene may also lead to developmental and epileptic encephalopathy.²⁶ It seems that both benign and severe epilepsies starting before 3 months of life are associated with missense mutations with a gain-of-function effect. The severity of the gain-of-function effect correlates with the severity of the clinical phenotype.²⁴

BFNIE associated with *SCN2A* presents with seizure between 2 days and 3-6 months of life. Although half of the patients present in the neonatal period, there is heterogeneity within the same family and different members with the same mutation may have a different age at onset. Seizures tend to occur in clusters and are predominantly focal tonic and focal clonic. The interictal EEG is normal or shows occasional focal spikes. Seizures abate within the first 2 years of life with low recurrence risk and good neurodevelopmental outcome.^{24,27}

On the other end of the spectrum, de novo missense variants in *SCN2A* can be associated with refractory epilepsy presenting in the first months of life. The predominant seizure types in these infants are focal tonic, tonic-clonic, or epileptic spasms. The initial EEG is abnormal with a suppression burst pattern or multifocal spikes. Patients have severe intellectual disability, axial hypotonia and microcephaly sometimes accompanied by a movement disorder.^{24,28} Analogous to the situation with *KCNQ2*, potential benefit of sodium channel blockers, such as carbamazepine and phenytoin, has been suggested.^{28,29}

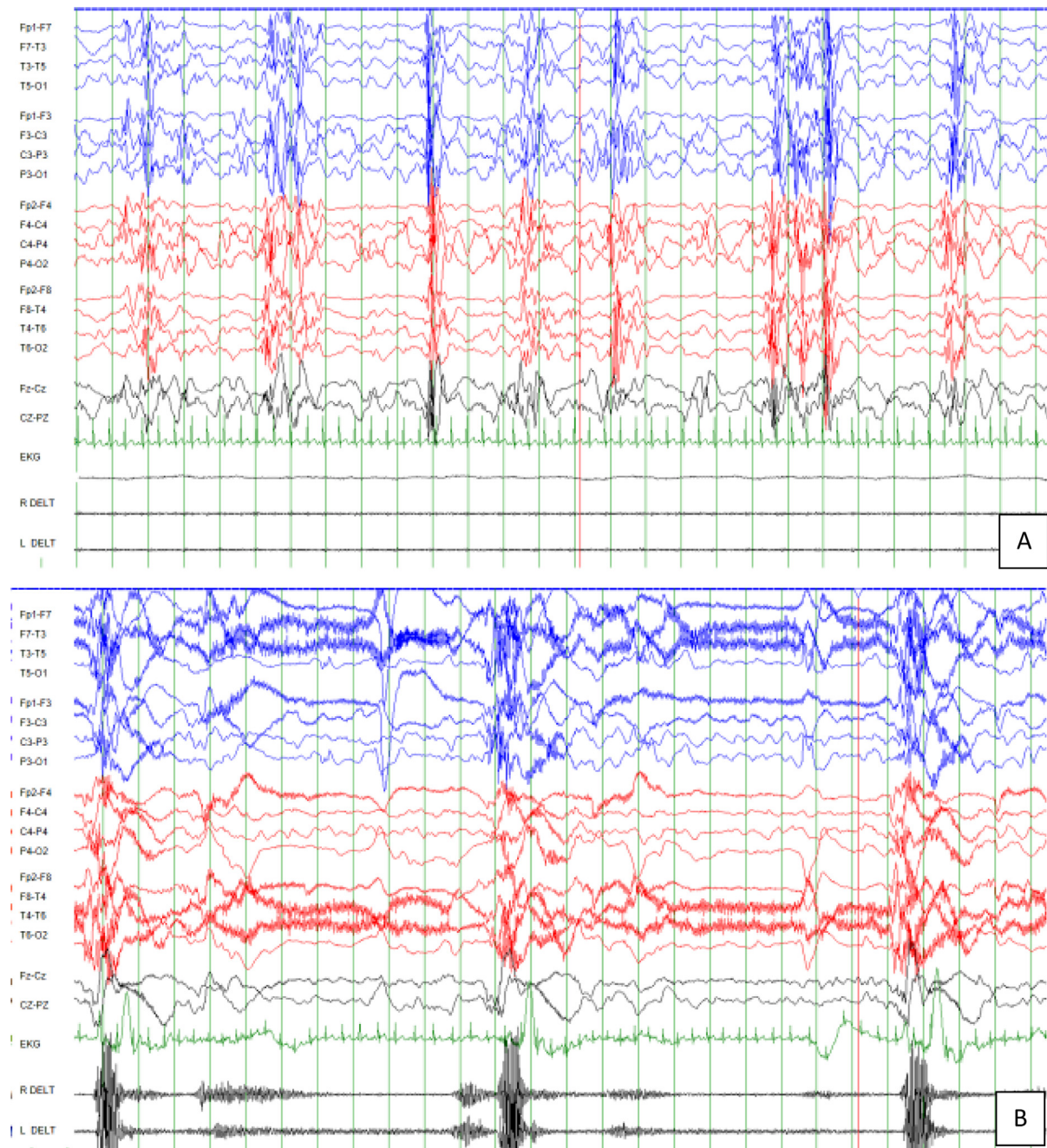


Figure 1 (A and B) Polygraphic EEG recording showing a burst-suppression pattern in a 4-week-old infant with Ohtahara syndrome with STXBP1 mutation, recorded during sleep (A) and wakefulness (B). The bursts consist of high-amplitude spikes and slow waves lasting 1-2 s and appearing synchronously over the 2 hemispheres, intermixed with periods of low-voltage activity. A cluster of tonic spasms during wakefulness is shown in (B), with the characteristic diamond shape of the EMG over the left and right deltoids associated with a diffuse high-amplitude slow wave on EEG and an altered respiratory pattern with chest movements occurring almost exclusively during the burst phase. The polygraphic recording demonstrates fragmentary low-amplitude myoclonic jerks involving both extremities and shifting randomly from one side to another. Gain 10 μ V/mm; high-frequency filter, 60 Hz; paper speed, 15 mm/s.

CDKL5 Encephalopathy

Pathogenic variants in the X-linked cyclin-dependent kinase like 5 (CDKL5) gene are responsible for early onset epilepsy associated with encephalopathy affecting mostly females and presenting frequently in the neonatal period. Some males

with very severe early onset phenotype or mosaicism for the pathogenic variant have also been reported.^{30,31}

Epilepsy starts at a median age of 6 weeks. At onset, seizures are tonic, brief but frequent and often intractable. They are associated with hypotonia and poor eye contact. During this early stage, the interictal EEG can remain normal. Some

of these infants experience successful seizure control after several weeks to months. Subsequently, the EEG background deteriorates, development stagnates, and seizures recur with a distinctive “hypermotor-tonic-spasms” sequence.³² Soon after awakening from sleep, the first part of the seizure begins with a hypermotor phase with rocking, kicking, and vocalization lasting 10–60 seconds, accompanied by diffuse delta activity. Low-voltage fast activity in the frontal-central regions bilaterally, presents during or precedes the hypermotor phase in half of patients. The second part of the sequence is marked by a tonic phase either with extension of all limbs or extension of the upper limbs and flexion of the lower limbs, lasting 20–45 seconds. The EEG may show attenuation with superimposed low-voltage fast activity in the frontocentral regions bilaterally. In the third part, the seizure evolves to a series of extensor spasms. Spasms are accompanied by high-voltage sharp slow complexes maximum in the frontocentral midline region, followed by attenuation.³²

Later on, children can evolve to multifocal and myoclonic epilepsy.^{16,33,34} Marked motor and cognitive impairment associated with feeding and sleep difficulties are typical.³⁵

No specific evidence-based treatment is established yet. It has been shown that a protein transduction domain (TAT) is able to deliver macromolecules into cells and even into the brain when fused to a given protein and recent studies showed that intracerebroventricular infusion of TAT-CDKL5 could restore hippocampal development, and reverse hippocampus-dependent memory loss and abnormal breathing patterns in CDKL5-null mice. Furthermore, systemically administered TAT-CDKL5 protein could pass the blood-brain barrier, improving various neuroanatomical and behavioral symptoms in the mouse, including breathing pattern and visual responses.³⁶

Epilepsy of Infancy With Migrating Focal Seizures

Epilepsy of infancy with migrating focal seizures (EIMFS) often presents in the neonatal period. It was first described by Coppola in 1995.³⁷ Seizures in EIMFS evolve over time. During the first phase of the disease, focal seizures with a unilateral motor onset may be sporadic. In half of the patients, seizures are associated with autonomic symptoms, such as apnea and desaturation, and are sometimes misdiagnosed as gastroesophageal reflux. During the second phase, that may already start in the first month of life, seizures become very frequent, occurring in clusters of 5–30 seizures several times a day or being almost continuous for days or weeks. Focal seizures may become bilateral and are associated with an autonomic component (cyanosis, bradycardia), hypotonia, and loss of consciousness. Seizures tend to be refractory to both conventional AEDs and corticosteroids. However, some response has been reported with potassium bromide³⁸ and levetiracetam.^{39,40} After 1–5 years, seizures become less frequent, but severe developmental disability persists.^{37,41} EEG shows multifocal paroxysmal abnormalities affecting alternatively both hemispheres with

migrating features characterized by multiple independent prolonged seizures evolving simultaneously from different regions of the brain.⁴¹

The most common cause of EIMFS is *de novo* gain-of-function mutations in KCNT1, encoding a sodium-activated potassium channel.^{41,42} This channel mediates the slow hyperpolarization that accompanies repetitive neuronal firing. Pathogenic mutations increase the current amplitude through enhanced cooperativity between individual channels.⁴³ Interestingly, quinidine, a class I antiarrhythmic drug, was found to reverse *in vitro* the increased conductance of KCNT1.⁴⁴ This led to trial of quinidine in a patient with reported efficacy.⁴⁵ However, treatment failures have also been reported, even when quinidine was started very early in the course of the disease.^{46,47}

The determinants of responsiveness to quinidine remain unclear, but may include genotype, dose, and route of administration and pharmacokinetics. Particularly, the clinical inefficacy observed may be due to inadequate tissue concentrations. Therapeutic serum levels of quinidine are 2–6 $\mu\text{g/mL}$. Cardiac toxicity can arise at any dose, but certainly at serum levels above 9 $\mu\text{g/mL}$. Therefore, further increases in serum levels are unlikely to result in adequate target tissue concentrations without significant cardiovascular side effects.⁴⁷ A better understanding of exposure and necessary receptor occupancy may tailor future *in vitro* assays to assess the efficacy of novel therapeutics at lower concentration ranges and predict clinical efficacy in patients with KCNT1 variants. While targeting of the KCNT1 channel with quinidine in EIMFS did not provide uniform benefit, genomic-guided therapy with potassium bromide may ameliorate the epileptic phenotype in this population, as patients who received potassium bromide were noted to have reductions in seizure frequency and severity.^{48,49}

STXBP1 Encephalopathy

De novo mutations in STXBP1 (syntaxin-binding protein 1) gene are responsible for a neonatal-onset developmental encephalopathy associated with epilepsy.⁵⁰ STXBP1 gene code a membrane-trafficking protein predominantly expressed in the brain, playing an important role in vesicular docking and fusion, a necessary mechanism for neurotransmitter secretion. Loss of function mutation in STXBP1 increases synaptic depression at both GABAergic and glutamatergic synapses with a greater impact on GABAergic interneurons resulting in net hyperexcitability and epileptic activity.⁵¹ Patients present with seizures generally with a focal motor component, usually tonic spasms in the first 3 months of life, and often in the neonatal period. EEG at onset is markedly abnormal, frequently showing a burst suppression pattern or multifocal abnormalities. Half of the patients evolve to West syndrome. They have moderate to severe cognitive impairment and normal head circumference.^{50,52} Seizures are refractory in the neonatal period and most patients are initially treated with multiple medications. Epilepsy may settle down relatively early in the child's history, but the

Table 1 Electroclinical Features of the Most Common Genetic Neonatal-onset Developmental and Epileptic Encephalopathies

Phenotype MIM number Transmission	Gene/ locus MIM number	Seizures Semiology	Interictal EEG	Ictal EEG	Treatment
<i>KCNQ2</i> -EE #613720 AD	<i>KCNQ2</i> 602235	Asymmetric tonic posturing Shifting laterality +/- clonic movement +/- apnea and desaturations	Lack of organization and multifocal epileptiform abnormalities	Low voltage fast activity, followed by recruiting spikes or theta rhythms, mainly in the central regions, followed by focal spike-wave complexes and focal or diffuse attenuation	- Carbamazepine - Oxcarbazepine - Phenytoin
<i>SCN2A</i> -EE #613721 AD	<i>SCN2A</i> 182390	Clusters of focal seizures with tonic component	Multifocal spikes or BS pattern	Focal or multifocal ictal patterns consisting of different rhythmic frequencies including fast rhythms.	- Carbamazepine - Phenytoin
<i>CDKL5</i> -EE #300672 X-linked dominant	<i>CDKL5</i> 300203	• Tonic seizures • Epileptic spasms • Hypermotor-tonic-spasms sequence • Prolonged tonic-clonic-myoclonic seizures (2.5 to 3 min)	Background can be initially normal than deteriorates into diffuse moderate to severe slowing and multifocal epileptiform abnormalities	Hypermotor-tonic-spasms: • Hypermotor: diffuse delta • Tonic: attenuation and low voltage fast activity or rhythmic delta waves • Spasms: high-voltage sharp slow complexes maximal in vertex followed attenuation Prolonged tonico-clonic-myoclonic seizures: • Tonic-clonic: initial build-up of rhythmic discharges of spikes and slow waves • Clonic-myoclonic: subsequent rhythmic sharp waves	No effective treatment
<i>KCNT1</i> -EE #614959 AD	<i>KCNT1</i> 608167	Focal seizures with tonic component and autonomic signs including apnea and desaturation	Multifocal epileptiform abnormalities and lack of organization of the background	Sub-continuous prolonged discharges migrating from one region to another and from one brain hemisphere to another	- Bromides - Levetiracetam - Quinidine (inconsistent efficacy)
<i>STXBP1</i> -EE #612264 AD	<i>STXBP1</i> 602926	Refractory epileptic spasms	BS pattern that can evolve into hypsarrhythmia	Epileptic spasms: bursts of high-amplitude spikes and slow waves	No effective treatment

AR: Autosomal recessive; AD: Autosomal dominant; BS: Burst suppression; EE: Epileptic encephalopathy.

developmental consequences may remain profound. Affected infants also tend to develop an ataxic gait and paroxysmal nonepileptic movements later in childhood.⁵²

Newly Described Early Onset Developmental and Epileptic Encephalopathies

In addition to the above-cited conditions (Table 1), other conditions show early onset developmental and epileptic encephalopathy through a multitude of pathways.

The GRIN1 mutations present with infantile-onset epilepsy, encephalopathy, hyperkinetic, and stereotyped movement disorders, with severe intellectual and communication disability. The epilepsy phenotype of GRIN1 mutation carriers seems variable with respect to age at onset (day of life 1–11 years), seizure semiology (infantile spasms, tonic and atonic seizures, hypermotor seizures, focal dyscognitive seizures, febrile seizures, generalized seizures, status epilepticus), and the associated EEG pattern (hypsarrhythmia, focal, multifocal and generalized spikes and waves).⁵³

In addition, GRIN2B through various potential gain-of-function and loss-of-function mechanisms is associated with neurodevelopmental disorders and a spectrum of symptoms, including hypotonia, movement disorders, cortical visual impairment, cerebral volume loss, and epilepsy. A retained sensitivity to the use of dependent blocker memantine needs to be demonstrated.⁵⁴

Recessive PTPN23 variants that encode a ubiquitously expressed nonreceptor type, catalytically inactive protein-tyrosine phosphatase found in all cells including neurons, are linked with severe early onset refractory epilepsy, global developmental delay, cortical blindness, hypomyelination and brain atrophy, and, in some cases, premature death. PTPN23 is one of the novel regulators of survival motor neuron function in the assembly of splicing factors (Uridine-rich small nuclear ribonucleoproteins, UsnRNPs).^{55,56}

Heterozygous mutations in ATP6V1A cause developmental encephalopathy with epilepsy evolving into encephalopathy with profound delay, hypotonic/dyskinetic quadriparesis, and intractable epilepsy with multiple seizure types in 50% of patients. ATP6V1A encodes the A subunit of v-ATPase, a multi-subunit proton pump that regulates pH homeostasis in all eukaryotic cells, and in neurons plays additional and unique roles in synapse function.⁵⁷

Conclusion

Developmental and epileptic encephalopathies regroup entities with genetic etiologies, with refractory epilepsy and severe impact on development.

Despite early control of epileptic seizures that may be obtained in some cases, patients with disorders related to the mutations cited above (KCNQ2, SCN2A, CDKL5, KCNT1, and STXBP1) suffer from severe developmental delay.

Genetics continues to reveal the different pathophysiology mechanisms leading to complex developmental epilepsy conditions.⁵⁸ Emergence of precision medicine, with medications targeting the main underlying pathophysiology is the pathway to bring a real improvement for these patients.

Concerted research efforts in the domains of genetics, epilepsy and neurosciences, will open the way for a better understanding of these conditions, especially of those encephalopathies that do not segregate uniformly with mutations. Early recognition of the electroclinical phenotypes and prompt genetic diagnosis still yield the best chances of targeted therapy in a window where we can truly exert changes to neurodevelopment.

Declaration of Competing Interest

The authors have no commercial, proprietary, or financial interest in any product described in this article.

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